FINAL

Report on Carcinogens Background Document for

Ethyl Acrylate

December 2 - 3, 1998

Meeting of the
NTP Board of Scientific Counselors
Report on Carcinogens Subcommittee

Prepared for the:
U.S. Department of Health and Human Services
Public Health Services
National Toxicology Program
Research Triangle Park, North Carolina 27709

Prepared by:
Technology Planning and Management Corporation
Canterbury Hall, Suite 310
4815 Emperor Boulevard
Durham, NC 27703
Contract Number NOI-ES-85421

Table of Contents

List of Tables

List of Figures

Summary Statement

Carcinogenicity

Ethyl acrylate was first listed in the National Toxicology Program (NTP) Fifth Annual Report on Carcinogens as *reasonably anticipated to be a carcinogen* based upon a gavage study resulting in dose-related forestomach benign and malignant neoplasms in rats and mice (NTP 1989).

Petition to Delist

In August 1997, the NTP was petitioned to delist ethyl acrylate from the Report on Carcinogens by the Basic Acrylic Monomer Manufactures, Inc. (BAMM), a trade association comprised of manufacturers of acrylic acid and acrylate esters, including ethyl acrylate. The BAMM petition to delist ethyl acrylate is based upon the following assertions: 1) negative tumorigenicity results from chronic studies using routes other than gavage in corn oil; 2) research results suggesting that the forestomach carcinogenicity observed in the gavage studies is secondary to a site-specific and concentration-dependent irritating effect of ethyl acrylate; and 3) that significant human exposure to ethyl acrylate monomer is unlikely in light of current manufacturing practices and patterns of usage.

Animal Studies

While ethyl acrylate is mutagenic in some *in vitro* tests, it is not genotoxic under *in vivo* physiological conditions perhaps due to its rapid metabolism to acrylic acid and ethanol by carboxyesterases and detoxification through binding to non-protein sulfhydryls. Target tissue toxicity, comprized of irritation, has been observed in the skin in a lifetime mouse skin painting study; in the nasal olfactory mucosa, in 27-month inhalation studies in rats and mice; and in the forestomach, in two-year corn oil gavage studies in rats and mice. Only body weight reduction was observed in a two-year dosed-water study in rats. The forestomach carcinogenicity observed in the corn oil gavage studies represents the only treatment-related tumorigenic response in the various animal studies. The irritation, hyperplasia, and tumor responses in the forestomach were related more to target tissue concentration of ethyl acrylate than to delivered dose in the chronic gavage study. Based upon stop-exposure studies, gavage doses of ethyl acrylate in corn oil sufficient to induce sustained mucosal hyperplasia in the forestomach must be administered for longer than six months to induce forestomach neoplasia.

Human Exposure and Cancer Risk

Prolonged consumer exposure to high levels of ethyl acrylate monomer by the oral route is unlikely. Potential significant exposures would most likely occur in an occupational setting where the routes of exposure would be dermal and inhalation. Ethyl acrylate has a strong acrid odor (odor threshold ~ 0.5 ppb) and is a known irritant to the skin, eyes, and mucous membranes, making it unlikely that humans would willingly be chronically exposed to high concentrations. Data provided in the BAMM petition on worker exposure show occupational exposure well below the threshold limit value (TLV=5 ppm for an eight-hour time-weighted average) and the

short-term exposure limit (STEL=15 ppm), although exposure of painters in an unventilated room has been reported as high as 8 ppm in the painter's breathing zone.

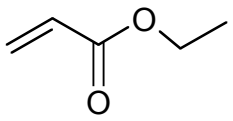
An epidemiology study reported on mortality from cancer of the colon and rectum in three separate cohorts of workers from two plants manufacturing and polymerizing acrylate monomers. Workers were exposed to ethyl acrylate and methyl methacrylate monomer between 1933 and 1982. Risks for both types of cancer were associated with exposure in the earliest cohort, although the rectal cancer results are imprecise because of the small number of cases involved. The greatest relative risk was found in workers with the highest level of exposure and a 20 year latency. The other two cohorts, with later dates of hire, showed no excess risk, but very few cases were available for observation. This study, by itself, can neither establish nor rule out a causal relationship of ethyl acrylate with cancer.

Recommendation

It is recommended that ethyl acrylate be *delisted* from the Report on Carcinogens because the forestomach tumors, induced in animal studies, were seen only when the chemical was administered by gavage at high concentrations of ethyl acrylate, that induced marked local irritation and cellular proliferation and because significant chronic human exposure to high concentrations of ethyl acrylate monomer is unlikely.

1 Physical and Chemical Properties

Figure 1-1. Ethyl Acrylate (CH2=CHCOOC2H5)



Ethyl acrylate ($C_5H_8O_2$, CASRN 140-88-5, Mol. Wt.=100.12) is also called:

Carbonyl ethylene

1-Propenoic acid ethyl ester

Ethyl propenoate

Acrylic acid ethyl ester

Ethoxycarbonylethylene

2-Propenoic acid ethyl ester

Ethyl 2-propenoate

Ethyl acrylate's RCRA waste number is U113 and, in shipping, its UN number is 1917.

Table 1-1. Physical—Chemical Properties

Property	Information	Reference
Molecular Weight	100.12	Budavari *et al.* (1996)
Color	Colorless	Hawley (1981), Sax (1989), Windholz (1983)
Physical State	Flammable liquid, easily polymerizes on standing	Budavari *et al.* (1996)
Melting Point at, ºC	-71.2	Weast (1985), Dean (1985)
Boiling Point at 760 mm, ºC	99.8	Weast (1986), Sax (1989)
Density at 20ºC/4ºC, g/mL	0.9234	Weast (1986)
Odor	Sharp acrid odor	Hawley (1981)
Solubility In water at 20ºC Organic Solvents Chloroform	 10-50mg/mL Soluble	Grasselli and Ritchey (1975), Hawley (1981), Weast (1985, 1986), Windholz (1983)

Property	Information	Reference
Ethanol Diethyl ether DMSO 95% Ethanol Acetone	Miscible Miscible ≥ 100mg/mL ≥ 100mg/mL ≥ 100mg/mL	
Vapor pressure at 20°C (mm Hg)	29	Sax (1989), Verschueren (1983)
Partition Coefficient Log octanol/water (Log P)	1.32	Hansch (1995)
Relative Vapor Density (air=1)	3.5	Verschueren (1983)
Flash Point °C	9	NIOSH (1981)

Ethyl acrylate (EA) spontaneously polymerizes on standing without the presence of an inhibitor. Inhibitors do not function in the absence of air. It is incompatible with oxidizers, peroxides, strong alkalies, acids, and polymerization initiators. Polymerization is accelerated by exposure to heat, peroxides, and light. High temperatures can negate the effects of inhibitors (MSDS 1989; Sittig 1985).

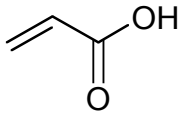
EA vapors form explosive mixtures in air (Hawley 1981; Windholz 1983) and can react vigorously with oxidizing materials. It is sensitive to exposure to moisture, light, and heat (MSDS 1989). EA reacts violently with chlorosulfonic acid (Sax 1989) and is subject to slow hydrolysis.

1.1 Identification of Structural Analogs and Metabolites

The major metabolite of EA is acrylic acid ($C_3H_4O_2$, CASRN 79-10-7, Mol. Wt.= 72.063). It is a clear colorless liquid. It is soluble in water, DMSO, 95% ethanol, and acetone (Miller *et al.* 1981).

The structure for acrylic acid is presented below:

Figure 1-2. Acrylic Acid (CH2=CHCOOH)



EA is metabolized by carboxylesterases (Silver and Murphy 1981; Stott and McKenna 1985; Udinsky and Frederick 1989) and by conjugation with glutathione (GSH) (Hashimoto and Aldridge 1970; Frederick *et al.* 1992). The mercapturic acid of EA has also been shown to be a minor urinary metabolite (deBethizy *et al*. 1987). It has also been proposed that EA binds to proteins and lipids *in vivo* (Ghanayem *et al*. 1987).

2 Human Exposure

2.1 Uses

Ethyl acrylate (EA) is used in various industries as an intermediate in the production of emulsion-based polymers. The major use for EA is in the manufacturing of acrylic resins, which are then used in paint formulations, industrial coatings, and latex products. EA is also used to manufacture polyacrylate elastomers, acrylic rubber, textile and paper coatings, leather finish resins, acrylic fibers, and in denture materials (HSDB 1997: telnet://toxnet.nlm.nih.gov/ ; http://sis.nlm.nih.gov; Radian 1991: http://ehis.niehs.nih.gov/ntp/chem_hs/ NTP_Chem1/ radian 140-88-5.txt).

EA is used to form paint coatings that is resistant to water, sunshine, and weather. These coatings retain flexibility even at low temperatures. EA is also used in industrial finishes and coatings for cans and coils. Fabrics gain texture and durability when EA is added during their manufacture. EA also imparts dirt resistance, improves abrasion, and binds pigments to fabric. Paper is coated with EA to make it water-resistant. Magazines, books, business paper, frozen-food packaging, and folding boxboards have such coatings, making them resistant to water, grease, and oil. EA is also used in adhesives for envelopes, labels, and decals. Caulk, glazing, and various sealants also contain EA. Leather products, such as automotive upholstery, furniture, clothing, and shoes contain EA so that topcoatings do not migrate. EA is also used as a fragrance additive in various soaps, detergents, creams, lotions, perfumes, and as a synthetic fruit essence (IARC 1986). EA is also found in such household items as nail mending kits and in medical items that assist with the binding of tissues, sealing wounds, and ileostomy appliances (Truett 1998: http://www.mc.vanderbilt.edu/vumcdept /derm/contact/ET007.html).

2.2 Production

Three companies in the United States produce EA: Hoechst Celanese Corp., Rohm & Haas, Co., and Union Carbide Corporation. In 1994, these three companies produced 165,515 kg of EA (USITC 1994). Production of EA has steadily increased during the 1990s (136,485 kg in 1990; 138,987 in 1991; and 152,680 kg in 1992) (USITC 1990, 1991, 1992). In 1989, the United States imported over 2.3 million pounds of EA while exporting 145.4 million pounds (USITC 1990, 1991, 1992) (EHIS 1998: http://ehis.niehs.nih.gov/roc/eighth/chemicals/ethacryl.pdf).

2.3 Environmental exposure

EA enters the environment mainly as a result of spills and industrial discharges. Human exposure to EA occurs mostly through inhalation of EA vapors, but it may also result from skin contact or drinking contaminated water. EA is highly soluble in water and is slightly persistent (half-life of 2-20 days). However, the majority of EA will dissipate and mix with the air (91%). EA also bioaccumulates in fish; with fish tissues analyzed having about the same average concentrations as the water they inhabit (U.S. EPA 1998: http://mail.odsnet.com/ TRIFacts/ 108.html).

EA biodegrades faster in air than in water. In the atmosphere, it undergoes photo-oxidative reduction with OH-radicals, and its half-life has been calculated at 13.7 hours. EA has also been qualitatively detected in the air of a landfill in the United States. EA can be readily absorbed into the ground, making it a very mobile compound (BUA 1995).

EA occurs naturally in some fruits: blackberries, raspberries, pineapples, and yellow passion fruit (BUA 1995). EA levels in these fruits are very low, with pineapples having EA concentrations of 0.77 mg/kg (IARC 1986).

2.4 Occupational exposure

In a polystyrene production plant, airborne EA concentrations at the breathing zone of workers and in the atmosphere of various workplaces are described in Table 2-1 and Table 2-2, respectively (Samimi and Falbo 1982).

Table 2-1. Time weighted average (TWA) concentrations of airborne EA at the breathing zone of workers in various job sites

Job Site	Number of Samples	Mean (ppb)	Range (ppb)
Reactor A	11	55	ND-274
Reactor B	9	ND	-
Reactor C	13	15	ND-60
Reactor D	6	ND	-
Unloading Docks	11	211	ND-844

Samimi and Falbo (1982)

ND=Non-detectable (<1ppb)

Table 2-2. Time weighted average (TWA) concentrations of EA in the atmosphere of various workplaces

Job Site	Number of Samples	Mean	Range (ppb)
Reactor A	8	3 ppb	ND-20 ppb
Reactor B	6	ND	-
Reactor C	6	10 ppb	ND-60 ppb
Reactor C (Lower Level)	9	27 ppb	ND-241 ppb
Reactor D	10	ND	-
Unloading Dock	18	3.1 ppm	ND-57 ppm[1]

Samimi and Falbo (1982)

ND=Non-detectable (<1ppb)

[1] EA was dripping due to a leaky hose

The mean TWA concentrations for EA was 0.06-0.2 mg/m^3 for personal breathing zones and 0.012-0.1 mg/m^3 for the work area (IARC 1986).

Data on EA concentrations in other work areas is limited. Table 2-3 summarizes other work environments that have been analyzed for EA concentrations.

Table 2-3. Time weighted average (TWA) concentrations of EA in the atmosphere of other work environments

Work Area	Sampling	Concentration of EA	Reference
Pilot Production and Processing Plant	Air	4-58 mg/m^3	Kuzelova *et al.* (1981)[1]
Resin Department of a Paint Manufacturing Facility	Air	<1-24 mg/m^3	Belanger and Coye (1981)[1]
Resin Manufacturing Plant	Air (from a scrubber stack)	49-2750 mg/m^3	Jones *et al.* (1981)[1]
Production Plant	Exhaust Gas	12,500-25,000 mg/m^3	BUA (1995)
Office Building	Indoor Air	0.04-2.1 mg/m^3	BUA (1995)

[1] Cited by the International Agency for Research on Cancer (IARC) (1986)

2.5 Ethyl Acrylate analysis and sampling

EA vapor sampling is the best method for determining environmental EA concentrations. National Institute of Occupational Safety and Health (NIOSH) approves of various collection tubes, with the best being a carbon disulfide tube. The tubes are then analyzed by gas chromatography. Biomarkers are not used because they cannot accurately be analyzed (NIOSH 1981: http://www.cdc.gov/niosh/81-123.html).

2.6 Regulations

EA is regulated by the U.S. Environmental Protection Agency (EPA) under the Comprehensive Environmental Response, Compensation and Liability Act (CERCLA); the Resource Conversation and Recovery Act (RCRA); and the Toxic Substances Control Act (TSCA). A reportable quantity (RQ) of 1,000 lb has been established under CERCLA for EA. RCRA has identified EA as a hazardous waste based on its ignitability, and subjects it to handling and report/record keeping requirements. FDA regulates EA as a component of synthetic flavorings and as a component of packaging that comes in contact with food. OSHA has revised the permissible exposure limit (PEL) to ≤5 ppm as an eight-hour time weighted average (TWA) with 25 ppm as the short-term exposure limit (STEL) for EA.

Table 2-4. EPA Regulations

EPA	
Regulatory Action	**Effect of Regulation/Other Comments**
40 CFR 172—Subpart B—Table of Hazardous Materials and Special Provisions. Promulgated: 55 FR 46798, 11/7/90.	Provides control of EA released into the environment. Final rule designates and establishes RQ of 1,000 lb (454 kg).
40 CFR 261—Subpart D—Lists of Wastes. Promulgated: 45 FR 33119, 05/19/80. Subjects waste products, off-specification batches, and spill residues in excess of 1,000 kg to handling and report/record	Designates EA as a hazardous constituent of waste, and subjects wastes known to contain it to the same requirements. As a result of the EPA Carcinogen Assessment Group's listing of EA as a potential carcinogen, it is regulated under the hazardous waste

EPA	
Regulatory Action	**Effect of Regulation/Other Comments**
keeping requirements.	disposal rule of RCRA.
40 CFR PART 302—Designation, Reportable Quantities, and Notification. Promulgated: 50 FR 13474, 04/04/85. U.S. Codes: 42 U.S.C. 9602, 9603, and 9604; 33 U.S.C. 1321 and 1361. EA is a hazardous material with a RQ of 1,000 lb (454 kg).	This regulation, under section 102(a) of the CERCLA of 1980, identifies reportable quantities for EA, and sets forth the notification requirements for releases of these substances. This regulation also catalogs reportable quantities for hazardous substances designated under section 311(b)(2)(A) of the Clean Water Act.
40 CFR PART 372—Toxic Chemical Release Reporting: Community Right-to-Know. Promulgated: 53 FR 4525, 02/16/88. U.S. Codes: 42 U.S.C. 11023 and 11048.	Details reporting and notification requirements for handlers of hazardous materials such as EA. General threshold amounts are 10,000 lb for toxic chemicals used at a facility and 25,000 lb/yr, if manufactured or processed at a facility.

Table 2-5. OSHA Regulations

OSHA	
Regulatory Action	**Effect of Regulation/Other Comments**
29 CFR 1910 SUBPART Z—Toxic and Hazardous Substances. Promulgated: 55 FR 9033 1/90. U.S. Codes: 29 U.S.C. 653, 655(a), and 657.	Sets forth an employee's exposure to EA based on respiratory effects (potential for skin adsorption noted). PEL $\leq$ 5 ppm (20 mg/m^3); STEL $\leq$ 25 ppm for 15 min.
29 CFR 1910.1200—Hazard Communication. Promulgated: 59 FR 6170, 02/09/94. U.S. Codes: 29 U.S.C. 653, 655, and 657.	Requires chemical manufacturers, importers, and all employers to assess chemical hazards and to provide information to employees. Hazard Communication Program will include labels, material safety data sheets, and worker training.
29 CFR 1910.1450—Occupational exposure to hazardous chemicals in laboratories. Promulgated: 01/31/90.	As a select carcinogen (IARC Group 2B), EA is included as a chemical hazard in laboratories. Employers are required to provide employee information and training, and to provide a Chemical Hygiene Plan.
29 CFR 1915 SUBPART Z—Toxic and Hazardous Substances. Promulgated: 58 FR 35514, 07/01/93.	Shipyard exposure to EA should not exceed 25 ppm (100 mg/m^3).
29 CFR 1926 SUBPART D—Occupational Health and Environmental Controls. Promulgated: 61 FR 9250, 03/03/96. U.S. Codes: 40 U.S.C. 333; 29 U.S.C. 653, 655, and 657.	Exposure of employees to inhalation, ingestion, skin absorption, or contact with EA must not exceed 25 ppm (100 mg/m^3) in construction settings.

Table 2-6. FDA Regulations

FDA	
Regulatory Action	**Effect of Regulation/Other Comments**
21 CFR 172.515—Synthetic flavoring substances and adjuvants. Promulgated: 61 FR 14245, 04/01/96.	EA may be used as a synthetic flavoring substance provided it is used in the minimum quantity required to produce its intended effect, and otherwise in accordance with all the principles of good manufacturing practice.
21 CFR 175—Indirect Food Additives: Adhesives and Components of Coatings. Promulgated: 42 FR 14534, 03/15/77. U.S. Codes: 21 U.S.C. 321, 342, 348, 379e.	EA may be safely used in adhesives that are components of articles intended for use in packaging, transporting, or holding food provided the adhesive is either separated from the food by a functional barrier or does not exceed the limits of good manufacturing practice.
21 CFR 176—Indirect Food Additives: Paper and Paperboard Components. Promulgated: 42 FR 14554, 03/15/77. U.S. Codes: 21 U.S.C. 321, 342, 346, 348, 379e.	EA may be safely used as components of the uncoated or coated food-contact surface of paper and paperboard intended for use in producing, manufacturing, packaging, processing, preparing, treating, packing, transporting, or holding aqueous and fatty foods, provided the amounts of EA used does not exceed that necessary to accomplish the technical effect.
21 CFR 177 SUBPART B—Substances for Use as Basic Components of Single and Repeated Use Food Contact Surfaces. Promulgated: 42 FR 14572, 03/15/77.	Semi-rigid and rigid acrylic, modified acrylic plastics, and cellophane made from EA may be safely used as articles intended for use in contact with food.
21 CFR 177 SUBPART C—Substances for Use Only as Components of Articles Intended for Repeated Use. Promulgated: 56 FR 42933, 08/30/91.	Cross-linked polyester resins and resin-bound filters made with EA may be safely used as articles or components of articles intended for repeated use in contact with food.
21 CFR 178 SUBPART D—Certain Adjuvants and Production Aids.	EA may be safely used mixed, alone, or in mixture with other permitted polymers, as modifiers in semi-rigid and rigid vinyl chloride plastic food-contact articles.
21 CFR 181.30—Substances used in the manufacture of paper and paperboard products used in food packaging. Promulgated: 42 FR 14638, 03/15/77. U.S. Codes: 21 U.S.C. 321, 342, 348, and 371.	EA may only be used in the manufacture of waxed paper and paperboard products used in food packaging.

3 Human Studies

No case reports or epidemiological studies were available for review in the IARC Monograph (1986) to evaluate the carcinogenicity of ethyl acrylate (EA) to humans. Similarly, no data were available to evaluate the reproductive effects or prenatal toxicity of ethyl acrylate to humans (IARC 1986).

3.1 Cohort Studies

A more recent study by Walker *et al*. (1991) evaluated the mortality from cancer of the colon or rectum among workers exposed to EA and methyl methacrylate (MMA). Three cohorts were assembled consisting of white male workers associated with acrylic sheet manufacturing facilities at Bristol, Pennsylvania (employed between 1933 and 1945); later at Bristol (hired between 1946 and 1982); and at Knoxville, Tennessee (employed between 1943 and 1982). All cohort members were traced until death or December 1986. The split in the Bristol cohort was due to changes in production methods. Following an explosion in 1943 at the EA production facility, the proportion of EA in the polymerization mixture was changed immediately from 12 to 6%, with a subsequent decline to zero in the following decade. However, EA was used elsewhere in the same buildings in which acrylic sheet was produced, even after its use in acrylic sheet production was discontinued completely.

The two cohorts (later Bristol and Knoxville), with later dates of hire, showed no excess mortality from any cause, including colon cancer or rectal cancer. In the earliest Bristol cohort, excess colon cancer seemed restricted to men employed extensively in the early 1940s in jobs entailing the highest exposures to vapor-phase EA and MMA monomer, and volatile by-products of the EA/MMA polymerization process. The excess mortality appeared 20 years after the equivalent of three years work in jobs with the most intense exposures. A smaller elevation in colon cancer mortality appeared in a low-exposure group in the early Bristol cohort. Rectal cancer mortality was elevated in the same categories that showed excess rates of colon cancer death; however, due to lower rates, the rectal cancer results are less precise.

The EA/MMA exposures of members of the three cohorts were estimated on the basis of job histories and job-specific exposure rating scales. Monitoring data for EA/MMA were available only from the Bristol plant beginning in 1972; earlier levels of exposure to EA/MMA were reconstructed from production records and interviews with plant personnel. The resulting exposure scales were semiquantitative, pertained to vapor exposure only, did not distinguish between EA and MMA, relied on the recollection of long-term employees, were not verifiable, were not mutually comparable across all three cohorts, and did not take into account the presence of other substances in the workplace. These other substances included some which have subsequently been considered as either probable or possible carcinogens by the IARC (lead, ethylene dichloride, methylene chloride, and acrylonitrile) (Walker *et al*. 1991).

3.2 Case-Control Studies

No data available to date.

Table 3-1. Post IARC (1986) Human Studies for Ethyl Acrylate

Design	Population Group	Exposure	Effects	Potential Confounders/Effects	Comments	Reference
cohort	Three cohorts working from 1933-1982 in two plants manufacturing and polymerizing acrylate monomers. Early Bristol: 3934 white males employed as hourly workers at any time between 1 January 1933 and 31 December 1945. Later Bristol: 6548 white males hired as hourly or salaried workers during the period 1 January 1946 to 31 December 1982. Knoxville: 3381 white males employed from 1 January 1943 to 31 December 1982. All cohort members were followed until death or 31 December 1986.	Exposure intensity scores zero (not exposed) to five. Total dose for each job derived by multiplying the exposure intensity by the interval in days from start to end of employment in the job, divided by 365.25.	Evaluation: Early Bristol colon cancer: 1) threshold analysis, 2) mutually exclusive dose categories at 20 years, 3) maximum exposure intensity, 4) date of hire, and 5) characteristics of decedents. Early Bristol rectal cancer: mutually exclusive accumulated dose categories. Later cohorts: accumulated EA/MMA dose at 20 years. Results: Early Bristol colon cancer: Excess colon cancer restricted to men employed in early 1940s in jobs entailing highest exposures to vapor-phase EA and MMA monomer and volatile by-products of the EA/MMA polymerization process. Excess mortality appeared 20 years after equivalent of three years work in jobs with most intense exposures. RR= 2.40 (95% CI 1.33-4.34). Smaller elevation in colon cancer mortality in low-exposure group in early cohort. Early Bristol rectal cancer: observed-to-expected ratio of 1.9	Exposures to other possible carcinogens.	Exposure unit was a cumulative score, such that long-term, low-dose exposure was not differentiated from short-term, high-dose exposure.	Walker *et al*. (1991)

Design	Population Group	Exposure	Effects	Potential Confounders/Effects	Comments	Reference
			(95% CI 0.92-3.4) 10 deaths were observed to 5.23 expected. In the second cohort of later Bristol workers there were few person years in the higher exposure categories. The mid-dose of 5-9 units resulted in RR =1.26 (95% CI 0.18-8.92). (One unit represents exposure for one year in a job with a dose rating of one, or six months in a job with a rating of two, or three months in a job with a rating of four.) Colon cancer showed no association with exposure and there were no rectal cancer cases. The third cohort of Knoxville workers showed an excess in colon cancer at the lowest exposure category RR=1.85 (95% CI 1.15-2.98), but deficits for the three higher exposure categories. There was only one case of rectal cancer with three cases expected.			

4 Experimental Carcinogenesis

The International Agency for Research on Cancer (IARC) assessed the carcinogenic potential of ethyl acrylate (EA) in 1986 (IARC 1986). The IARC Working Group reviewed rodent studies reporting EA exposures via oral, dermal, and respiratory routes.

4.1 Previously reviewed studies

Young Wistar rats (groups of 25 males and 25 females) were administered 0, 6-7, 60-70, or 2000 ppm EA in the drinking water (estimated to be 10, 100, or 3000 ppm in food based on observed fluid and food consumption). Surviving rats were sacrificed at two years of age. Body weights at 2000 ppm EA in water were depressed or significantly depressed throughout the study for females and through the first year for males. Mortality was unaffected. No evidence of systemic toxicity, nor carcinogenicity was observed (Borzelleca *et al*. 1964). The IARC Working Group noted incomplete reporting of this study's findings (IARC 1986).

The National Toxicology Program (NTP 1986: http://ehis.niehs.nih.gov/ntp/chem_ hs/NTP _ Chem1/radian140-88-5.txt) reported EA administered by gavage in corn oil (five doses per week for up to 103 weeks) caused both neoplastic and non-neoplastic lesions in the forestomachs of Fischer 344/N rats and $B6C3F_1$ mice. EA was given at levels of 0, 100, or 200 mg/kg. Non-neoplastic, forestomach lesions in both species included hyperkeratosis, hyperplasia, and inflammation. These changes were associated with dose-related increases in the incidences of squamous cell carcinoma, squamous cell papilloma, and squamous cell carcinoma and papilloma (combined) as shown in Table 4-1.

Table 4-1. Comparison of forestomach tumors in rats and mice based on Ethyl Acrylate concentration (a) in the corn oil gavage solution

	Squamous Cell Papilloma				Squamous Cell Carcinoma				Papilloma & Carcinoma			
	0%	1%	2%	4%	0%	1%	2%	4%	0%	1%	2%	4%
Rats												
Males	1/50	--	15/50	29/50	0/50	--	5/50	12/50	1/50	--	18/50	36/50
Females	1/50	--	6/50	9/50	0/50	--	0/50	2/50	1/50	--	6/50	11/50
Mice												
Males	0/48	4/47	9/50	--	0/48	2/47	5/50	--	0/48	5/47	12/50	--
Females	1/50	4/49	5/48	--	0/50	1/49	2/48	--	1/50	5/49	7/48	--

NTP (1986)

0% = vehicle controls; 1% = low dose mice (100 mg/kg); 2% = high dose mice (200 mg/kg) and low dose rats (100 mg/kg); 4% = high dose rats (200 mg/kg).

-- = not applicable

Forty male C3H/HeJ mice (74-79 days of age at start of study) were treated with 25 μL of undiluted EA (approximately 23 mg per application) thrice weekly to the dorsal skin for their complete lifespan. No statistically significant effects on survival were observed. The treatments also failed to influence the incidence of skin tumors in these animals, although histologic

evidence of skin irritation was noted in a few mice. The positive control treatment (0.1% 3-methylcholanthrene) elicited an unequivocally positive skin tumor response (33 confirmed squamous cell carcinomas) in 39/40 mice (DePass *et al*. 1984).

EA was administered by inhalation to Fischer 344 rats and $B6C3F_1$ mice (initial concentrations were 100, 310, and 920 mg/m^3). These animals were exposed to EA six hours a day, five days a week. Exposures to 100 and 310 mg/m^3 continued for 27 months. After six months, exposure to 920 mg/m^3 was terminated due to excessive weight loss in experimental rats and mice. Animals exposed to this highest EA concentration for six months were observed an additional 21 months. Treatment-related carcinogenicity was not evident in either species at the conclusion of the study. Non-neoplastic changes observed in treated rats and mice included olfactory mucosal glandular and basal cell hyperplasia and metaplasia. A follow-up study in which Fischer 344 rats and $B6C3F_1$ mice were exposed to 5 ppm (20 mg/ m^3) EA for 24 months revealed no treatment-related changes in the nasal mucosa (Miller *et al.* 1985).

4.2 Findings of earlier review groups

The IARC's Working Group concluded that there is sufficient evidence for the carcinogenicity of EA in experimental animals (IARC 1986). In the Annual Report on Carcinogens, NTP concluded that EA could reasonably be anticipated to be carcinogenic (ROC 1998: http://ehis.niehs.nih.gov/cgi-bin/roc.cgi).

4.3 Pertinent information developed since earlier reviews

Review of the scientific database on the toxicity and carcinogenicity of EA revealed no new classical carcinogenicity studies. Studies useful in understanding the carcinogenic potential of EA have been reported.

4.3.1 Ethyl Acrylate induced local toxicity at the site of application

The forestomach proliferative response of rats to EA administered by gavage has been shown secondary to local irritation at the site of administration of the chemical (see experimental descriptions in Section 6.1). Prolonged EA exposure (up to 12 months) as a corn oil gavage may result in increased incidences of squamous cell papillomas and/or carcinomas. Shorter regimens of administration, followed by recovery periods, result in time-related regression of proliferative changes of forestomach epithelium.

4.3.2 Testing in transgenic rodents

EA was tested in one transgenic mouse model (Tennant *et al*. 1996). When applied to the shaved dorsal skin of Tg.AC mice (three times per week for 20 weeks), EA did not cause the development of papillomatous lesions. The Tg.AC mouse is believed to respond to dermal applications of either genotoxic or non-genotoxic carcinogens with a rapid production of papillomas in the site of repeated applications.

In this regard, Tice *et al.* (1997) reported that application of EA to the shaved dorsal skin of Tg.AC mice (for up to 20 weeks) did not induce leukocytic DNA damage, nor did it increase the incidence of micronucleated erythrocytes. This absence of evidence of genotoxicity is consistent with a failure of Tg.AC mice to respond to repeated administrations of EA. However, failure of

the Tg.AC mice to respond to EA may also indicate that the dermal absorption of the chemical was simply insufficient to elicit expression of the transgene.

The use of transgenic models for carcinogen identification is in developmental stages. Accordingly, the failure of these animals to respond to EA, although suggestive, cannot be taken as conclusive evidence for a lack of carcinogenic potential.

5 Genotoxicity

5.1 Summary

The genotoxicity of ethyl acrylate (EA) has been investigated extensively in both *in vitro* and *in vivo* assays. The *in vitro* assays demonstrate that EA can induce DNA damage including chromosomal aberrations and gene/point mutations. When tested *in vivo*, EA was found to be nonmutagenic in systems measuring both the induction of chromosomal damage and induction of gene/point mutations. The lack of mutagenicity *in vivo* is consistent with data in rats on its rapid metabolism by hydrolysis to acrylic acid (IARC 1986). Thus, EA has mutagenic potential for the induction of chromosomal damage that is not fulfilled *in vivo* due to its rapid metabolism. In conclusion, the *in vitro* and *in vivo* data on the genotoxity of EA are consistent with the interpretation that EA should be considered non-genotoxic to exposed human populations.

5.2 Prokaryotic systems

5.2.1 Gene mutations

A number of reports have indicated that EA is not mutagenic to *Salmonella typhimurium* strains TA98, TA100, TA1535, TA1537, or TA1538 in the presence or absence of a metabolic activation system (S9) derived from the liver of polychlorinated biphenyl-induced rats and hamsters or phenobarbital-induced rats, when tested in liquid incubation and plate incorporation assays (Ishidate *et al*. 1981; Haworth *et al.* 1983; Tennant *et al.* 1987; Waegemaekers and Bensink 1984; Zeiger *et al.* 1992).

EA induced respiratory-deficient mutations in the yeast *Saccharomyces cerevisiae* (Zimmermann and Mohr 1992).

5.2.2 Other effects

EA induced chromosome malsegregation and mitotic recombination in the yeast *Saccharomyces cerevisiae* (Zimmermann and Mohr 1992).

5.3 Lower eukaryotic systems

5.3.1 Drosophila melanogaster

EA did not induce sex-linked recessive lethal mutations in *Drosophila melanogaster* (fruit flies) when administered in feed at 40,000 ppm or given at 20 mg/mL by injection (Valencia *et al*. 1985).

5.4 Mammalian systems *in vitro*

5.4.1 Chromosomal aberrations

EA induced a dose-related increase in the incidence of chromosomal aberrations in Chinese hamster lung cells in the absence of any added metabolic activation system (Ishidate 1983).

Chromosome aberrations and sister chromatid exchange were induced by EA in Chinese hamster ovary cells in the presence, but not in the absence, of added metabolic activation (Loveday *et al*. 1990).

EA induced chromosome aberrations in mouse lymphoma cells in the absence of added metabolic activation (Moore *et al*. 1988).

No significant increases in sister chromatid exchange frequency were observed when spleen cells taken from C57BL/6 mice were exposed to EA either during the G^0 stage of the cell cycle or 23 hours after mitogen stimulation during the late G^1 or early S phase of the cell cycle. Significant increases in chromatid-type aberrations were found when the target cells were treated 23 hours after mitogenic stimulation (Kligerman *et al*. 1991).

5.4.2 Gene mutations

EA consistently induced mutations in mouse lymphoma cells in the absence (Moore *et al*. 1988; Ishidate *et al.* 1981; McGregor *et al.* 1988; Moore *et al.* 1991; Tennant *et al*. 1987) or presence (Dearfield *et al.* 1991) of added metabolic activation. However, it did not induce mutations in Chinese hamster ovary cells, in the absence of added metabolic activation (Moore *et al.* 1991).

5.4.3 Cell transformation

EA induced cell transformation in cultured tracheal cells taken from rats (Steele *et al*. 1989).

5.5 Mammalian systems i*n vivo*

5.5.1 DNA damage

The alkaline single cell gel (known as SCG or Comet) assay was used to study peripheral blood leukocyte DNA from groups of female Tg.AC transgenic mice treated dermally with 60, 300, or 600 μM EA, three times per week for 20 weeks. Blood was taken every four weeks during treatment. DNA migration and dispersion in treated groups was not significantly affected by EA exposure as described. The experimental conditions applied (sufficient to induce local keratinocyte proliferation) failed to cause genotoxicity, as defined by the Comet Assay, or micronuclei (mentioned below). The authors suggested that EA is either not genotoxic or not absorbed through the skin sufficiently to cause measurable systemic effects (Tice *et al.* 1997).

No DNA adducts were detected in the forestomach or liver of groups of three male Fisher 344 rats given EA at doses up to 400 mg/kg by stomach tube (Ghanayem *et al*. 1987).

5.5.2 Gene mutations

To date, there are no peer reviewed reports of gene mutations detected after EA exposure in mammalians.

5.5.3 Chromosomal aberrations

No significant increases in chromosomal aberrations or sister chromatid exchange were found in the spleen cells of groups of five male C57BL/6 mice given EA at 125, 250, 500, or 1000 mg/kg by weight, in saline, by intraperitoneal injection (Kligerman *et al*. 1991).

5.5.4 Micronuclei

Groups of four male Balb/c mice were given two intraperitoneal injections (24 hours apart) of EA (total dose, 225-1800 mg/kg bw), and the bone marrow cells were examined six hours after

the second injection. A dose-related increase in the number of micronucleated polychromatic erythrocytes was observed (Przybojewska *et al*. 1984).

A repeat of this experiment, using groups of ten mice of strains C57BL/6 and Balb/c (*i.e*. including the strain used by Przybojewska *et al*. 1984) and two intraperitoneal doses, each up to 738-812 mg/kg, found no increase in the frequency of micronuclei in the bone marrow. The investigators noted that the purity of the material tested by Przybojewska *et al*. was not reported (Ashby *et al*. 1989).

When groups of five male C57BL/6 mice were given a single intraperitoneal injection of EA at 125, 250, 500, or 1000 mg/kg by weight a small but statistically significant increase in micronuclei was found at the highest dose. This was, however, apparently due to an elevated frequency in a single animal (Kligerman *et al.* 1991).

In more recent studies, no increases in micronuclei frequency were observed in the bone marrow of groups of six male BDF1 mice given a single intraperitoneal injection of EA at 375, 500, 750, or 1000 mg/kg. In addition, no positive effects were seen when doses of 188, 375, 750, or 1000 mg/kg were delivered by stomach tube (Morita *et al.* 1997).

The frequency of micronuclei among peripheral blood polychromatic and normochromatic erythrocytes did not increase in groups of female Tg.AC mice treated dermally with EA (as described above in Section 5.5.1) (Tice *et al.* 1997).

5.5.5 Other studies

Female mice of the Tg.AC line failed to respond (*i.e.* skin papillomas did not develop) to the dermal application of EA. Unfortunately, experimental details were not presented in this report (Tennant *et al*. 1996).

6 Other Data Relevant to an Evaluation of Carcinogenicity and its Mechanisms

6.1 Toxic effects of Ethyl Acrylate on forestomach epithelium

Gavage administration of ethyl acrylate (EA) during the National Toxicology Program (NTP) sponsored carcinogenicity studies in Fischer 344/N rats and $B6C3F_1$ mice caused dose-related, non-neoplastic changes in the forestomachs (non-glandular portion) in both sexes of both species (NTP 1986). Non-neoplastic lesions (hyperkeratosis, hyperplasia, and inflammation) were produced in pre-chronic studies by the administration of daily gavage doses of 400-800 mg/kg.

Ghanayem *et al*. (1985) reported that EA produced dose- and time-related stomach lesions after only two to four daily gavage doses of 200 mg/kg each. EA caused mucosal edema associated with vesicle formation, mucosal hyperplasia, submucosal edema and inflammation, and vacuolization of the tunica muscularis of the forestomach. Oral administrations of EA also caused submucosal edema and inflammation in the glandular stomach, and mucosal erosions or ulcers in both portions of the stomach. The administration of equivalent doses of EA by the subcutaneous or intraperitoneal routes did not produce gastric lesions. The absence of systemic toxicity and the dependency of gastric lesions on the gavage route of administration suggests that a localized response to an injurious agent at the site of application mediates the proliferative response.

The same researchers also reported, after repeated oral administrations of EA, the glandular portion of the rat stomach becomes refractory to the local toxicity produced by the chemical. Glandular portions of stomach were normal after 14 consecutive days of repeated administrations of 100 mg/kg. Adaptation of the forestomach, however, was proliferative in nature and featured papillomatous thickening. Cessation of EA administration for two weeks after 14 consecutive daily administrations of 100 mg/kg resulted in normalization of the forestomach epithelium (Ghanayem *et al*. 1986a, 1986b).

Reversibility of forestomach lesions after 13 weeks of oral EA administration has also been demonstrated (Ghanayem *et al*. 1991). Rats killed at the conclusion of 13 weeks of daily dosing with 100 or 200 mg/kg of EA exhibited severe hyperplasia of the forestomach epithelium but no lesions in the glandular stomach. Rats afforded an eight-week recovery period after the 13-week dosing regimen exhibited a significant decline in incidence and severity of mucosal cell hyperplasia relative to animals that had been sacrificed at the end of 13 weeks. Rats given a 19-month recovery period exhibited still more normalization of forestomach epithelium.

The sustainability of forestomach hyperplasia is apparently dependent upon the continued exposure of rats to EA. The authors noted that, although sufficient post treatment time was allowed for the development of forestomach tumors (up to 19 months after 13 weeks of dosing), there was nearly complete normalization of tissues. No increase in incidences of either squamous cell papilloma or carcinoma was observed. The results of this experiment are consistent with the absence of a genotoxic effect of EA in *in vivo* mammalian systems. Finally (Ghanayem *et al*. 1994) assessed the temporal relationship between EA-induced forestomach epithelial proliferation and carcinogenicity. EA was administered at 200 mg/kg, five days per week, to male Fischer 344 rats. Squamous cell proliferation was observed in the forestomachs of all rats

that had received EA for either 6 or 12 months. Cessation of dosing at 12 months followed by a two-month recovery resulted in squamous cell papillomas in 2/5 (40%) rats. In rats dosed for 12 months, then observed for nine months, squamous cell carcinomas or papillomas were observed in 4/13 (31%). In contrast, rats dosed with EA for six months and allowed a 2- or 15-month recovery, exhibited a time dependent regression of cell proliferation. They did not exhibit forestomach neoplasms. Thus, a temporal relationship exists between EA-induced epithelial cell proliferation and forestomach carcinogenicity.

7 References

1. Ashby, J., C.R. Richardson, and H. Tinwell. 1989. Inactivity of ethyl acrylate in the mouse bone marrow micronucleus assay. *Mutagenesis.* 4:283-285.

2. Belanger, P.L., and M.J. Coye. 1981. Health Hazard Evaluation. *Sinclair Paint Company and CA (US NTIS PB82-214396).* HHE-80-68-82. Washington, DC.

3. Borzelleca, J.F., P.S. Larson, J.R. Hennigarer, E.G. Hur, E.M. Crawford, and J.R. Smith. 1964. Studies on the Chronic Oral Toxicity of Monomeric Ethyl Acrylate and Methyl Methacrylate. *Toxicol.Appl.Pharmacol.* 6:29-36.

4. BUA (Beratergremium fuer umweltrelevante Altstoffe). 1995. *Ethyl Acrylate.* 128:105.

5. Budavari, S., M.J. O' Neil, A. Smith, and P.E. Heckelman, eds. 1996. *The Merck Index*. Rahway: Merck & Company, Inc.

6. Dean, J.A. ed. 1985. *Lange's Handbook of Chemistry*. New York: McGraw-Hill Book Company.

7. Dearfield, K.L., K. Harrington-Brock, C.L. Doerr, J.R. Rabinowitz, and M.M. Moore. 1991. Genotoxicity in mouse lymphoma cells of chemicals capable of Michael addition. *Mutagenesis.* 6:519-525.

8. deBethizy, J.D., J.R. Udinsky, H.E. Scribner, and C.B. Frederick. 1987. The disposition and metabolism of acrylic acid and ethyl acrylate in male Sprague-Dawley rats. *Fundam.Appl.Toxicol.* 8:549-561.

9. DePass, L.R., E.H. Fowler, D.R. Meckley, and C.S. Weil. 1984. Dermal oncogenicity bioassays of acrylic acid, ethyl acrylate, and butyl acrylate. *J.Toxicol.Environ.Health* 14:115-120.

10. EHIS (Environmental Health Information Service). 1998. Ethyl Acrylate CAS No. 140-88-5. *Report on Carcinogenesis, Eighth Edition.* http://ehis.niehs.nih.gov/roc/eighth/chemicals/ethacryl.pdf.

11. Frederick, C.B., D.W. Potter, M.I. Chang-Mateu, and M.E. Andersen. 1992. A physiologically based pharmacokinetic and pharmacodynamic model to describe the oral dosing of rats with ethyl acrylate and its implications for risk assessment. *Toxicol Appl.Pharmacol.* 114:246-260.

12. Ghanayem, B.I., L.T. Burka, and H.B. Matthews. 1987. Ethyl acrylate distribution, macromolecular binding, excretion, and metabolism in male Fisher 344 rats. *Fundam.Appl.Toxicol.* 9:389-397.

13. Ghanayem, B.I., R.R. Maronpot, and H.B. Matthews. 1985. Ethyl acrylate-induced gastric toxicity. I. Effect of single and repetitive dosing. *Toxicol.Appl.Pharmacol*. 80:323-335.

14. Ghanayem, B.I., R.R. Maronpot, and H.B. Matthews. 1986a. Association of chemically induced forestomach cell proliferation and carcinogenesis. *Cancer Lett*. 32:271-278.

15. Ghanayem, B.I., R.R. Maronpot, and H.B. Matthews. 1986b. Ethyl acrylate-induced gastric toxicity. III. Development and recovery of lesions. *Toxicol.Appl.Pharmacol*. 83:576-583.

16. Ghanayem, B.I., H.B. Matthews, and R.R. Maronpot. 1991. Sustainability of forestomach hyperplasia in rats treated with ethyl acrylate for 13 weeks and regression after cessation of dosing. *Toxicol.Pathol*. 19:273-279.

17. Ghanayem, B.I., I.M. Sanchez, H.B. Matthews, and M.R. Elwell. 1994. Demonstration of a temporal relationship between ethyl acrylate-induced forestomach cell proliferation and carcinogenicity. *Toxicol.Pathol.* 22:497-509.

18. Grasselli, J.G., and W.M. Ritchey, (eds.) 1975. *CRC Atlas of Spectral Data and Physical Constants for Organic Compounds*. Cleveland: CRC Press.

19. Hansch, C. 1995. *Exploring QSAR*. Washington, D. C.: Amer.Chem.Soc.

20. Hashimoto, K., and W.N. Aldridge. 1970. Biochemical studies on acrylamide, a neurotoxic agent. *Biochem.Pharmacol.* 19:2591-2604.

21. Hawley, G.G. 1981. *The Condensed Chemical Dictionary*. New York: Van Nostrand Reinhold Company, Inc.

22. Haworth, S., T. Lawlor, K. Mortelmans, W. Speck, and E. Zeiger. 1983. Salmonella mutagenicity test results for 250 chemicals. *Environ.Mutagen.* 5 Suppl 1:1-142.

23. HSDB (Hazardous Substance Data Bank). 1997. National Library of Medicine Specialized Information Services. telnet://toxnet.nlm.nih.gov/;http://sis.nlm.nih.gov

24. IARC (International Agency for Research on Cancer). 1986. Some Chemicals used in Plastics and Elastomers. *IARC Evaluation of the Carcinogenic Risk of Chemicals to Humans.* Vol 39, Sup 7: 81-98.

25. Ishidate, M. 1983. *The Data Book of Chromosomal Aberation Tests in Vitro on 587 Chemical Substances Using a Chinese Hamster Fibroblast Cell Line (CHL Cells)*. Tokyo: The Realize Inc.

26. Ishidate, M., T. Sofuni, and K. Yoshikawa. 1981. Chromosomal aberration tests in vitro as a primary screening tool for enviromental mutagens and/or carcinogens. *GANN Monograph on Cancer Research*, Division of Mutagenesis, Biological Safety Research Center, National Institute of Hygienic Sciences 27:95-108.

27. Jones, M.T., R.C. Pilgrim, and P.J. Murrow. 1981. Control of Acrylic Monomer Emissions from a Process Situated in a Sensitive Area. In *Proceedings of the Seventh International*

Clean Air Conference, *Adelaide, Australia*, edited by Webb, K., and A.J. Smith, 809-827. Ann Arbor: Ann Arbor Science.

28. Kligerman, A.D., A.L. Atwater, M.F. Bryant, G.L. Erexson, P. Kwanyuen, and K.L. Dearfield. 1991. Cytogenetic studies of ethyl acrylate using C57BL/6 mice. *Mutagenesis.* 6:137-141.

29. Kuzelova, M., J. Kovarik, D. Fiedlerova, and A. Popler. 1981. Screening of Fragrance Materials for Allergenicity in the Guinea Pig. I. Comparison of Four Testing Methods. *Pracov.Lek*. 33:95-99.

30. Loveday, K.S., B.E. Anderson, M.A. Resnick, and E. Zeiger. 1990. Chromosome aberration and sister chromatid exchange tests in Chinese hamster ovary cells in vitro. V: Results with 46 chemicals. *Environ.Mol.Mutagen*. 16: 272-303.

31. McGregor, D.B., A. Brown, P. Cattanach, I. Edwards, D. McBride, C. Raich, and W.J. Caspary. 1988. Responses of the l5178Y tk+/tk- mouse lymphoma cell forward mutation assay: III. 72 coded chemicals (published erratum). *Environ Mol Mutagen.* 12(3):345.

32. Miller, R.R., J.A. Ayres, L.W. Rampy, and M.J. McKenna. 1981. Metabolism of acrylate esters in rat tissue homogenates. *Fundam.Appl.Toxicol.I* 6:410-414.

33. Miller, R.R., J.T. Young, R.J. Kociba, D.G. Keyes, K.M. Bodner, L.L. Calhoun, and J.A. Ayres. 1985. Chronic toxicity and oncogenicity bioassay of inhaled ethyl acrylate in Fischer 344 rats and B6C3F1 mice. *Drug Chem.Toxicol.* 8:1-42.

34. Moore, M.M., A. Amtower, C.L. Doerr, K.H. Brock, and K.L. Dearfield. 1988. Genotoxicity of acrylic acid, methyl acrylate, ethyl acrylate, methyl methacrylate, and ethyl methacrylate in L5178y mouse lymphoma cells. *Environ.Mol.Mutagen*. 11:49-63.

35. Moore, M.M., L. Parker, J. Huston, K. Harrington-Brock, and K.L. Dearfield. 1991. Comparison of mutagenicity results for nine compounds evaluated at the hgprt locus in the standard and suspension cho assays. *Mutagenesis.* 6:77-85.

36. Morita, T., N. Asano, T. Awogi, Y.F. Sasaki, S. Sato, H. Shimada, S. Sutou, T. Suzuki, A. Wakata, T. Sofuni, and M. Hayashi. 1997. Evaluation of the rodent micronucleus assay in the screening of IARC carcinogens (groups 1, 2A and 2B) the summary report of the 6th collaborative study by CSGMT/JEMS MMS. Collaborative Study of the Micronucleus Group Test. Mammalian Mutagenicity Study Group (published erratum). *Mutat. Res.* 391(3):259-67, 389:3-122.

37. MSDS (Material Safety Data Sheets Service). 1989. Information Handling Services. Microfiche Ed. Bimonthly Updates.

38. NIOSH (National Institute of Occupational Safety and Health). 1981. NIOSH/OSHA Occupational Health Guidelines for Chemical Hazards. Publication No. 81-123(2). 1-1981.

Internet, U.S. Department of Health and Human Services and U.S. Department of Labor. http://www.cdc.gov/niosh/81-123.html.

39. NTP (National Toxicology Program). 1986. Carcinogenesis Studies of Ethyl acrylate (CAS 140-88-5) In F344/N Rats and B6C3F1 mice (Gavage Studies). National Toxicology Program, Technical Report Series No. 259. http://ehis.niehs.nih.gov/ntp/chem_hs/NTP_Chem1/radian140-88-5.txt

40. NTP (National Toxicology Program). 1989. *Fifth Annual Report on Carcinogens*.

41. Przybojewska, B., E. Dziubaltowska, and Z. Kowalski. 1984. Genotoxic effects of ethyl acrylate and methyl acrylate in the mouse evaluated by the micronucleus test. *Mutat.Res.* 135:189-191.

42. Radian. 1991. NTP Chemical Repository, Radian Corporation. http://ehis.niehs.nih.gov/ntp/chem_hs/NTP_Chem1/radian140-88-5.txt

43. ROC (Report on Carcinogens). 1998. Ethyl Acrylate. http://ehis.niehs.nih.gov/cgi-bin/roc.cgi

44. Samimi, B., and L. Falbo. 1982. Monitoring of workers exposure to low levels of airborne monomers in a polystyrene production plant. *Am.Ind.Hyg.Assoc.J.* 43:858-862.

45. Sax, N.I. 1989. *Dangerous Properties of Industrial Materials*. New York: Van Nostrand Reinhold Company, Inc.

46. Silver, E. H., and S.D. Murphy. 1981. Potentiation of acrylate ester toxicity by prior treatment with carboxylesterase inhibitor triorthotolyl phosphate (TOTP). *Toxicol.Appl.Pharmacol.* 57:271-278.

47. Sittig, M. 1985. *Handbook of Hazardous Chemicals and Carcinogens*. 2d ed. Park Ridge: Noyes Publications.

48. Steele, V.E., J.T. Arnold, J. Van Arnold, and M.J. Mass. 1989. Evaluation of a rat tracheal epithelial cell culture assay system to identify respiratory carcinogens. *Environ.Mol.Mutagen.* 14:48-54.

49. Stott, W.T., and M.J. McKenna. 1985. Hydrolysis of several glycol ether acetates and acrylate esters by nasal mucosal carboxylesterase in vitro. *Fundam.Appl.Toxicol*. 5:399-404.

50. Tennant, R.W., B.H. Margolin, M.D. Shelby, E. Zeiger, J.K. Haseman, J. Spalding, W. Caspary, M. Resnick, S. Stasiewicz, and B. Anderson. 1987. Prediction of chemical carcinogenicity in rodents from in vitro genetic toxicity assays. *Science.* 236:933-941.

51. Tennant, R.W., J. Spalding, and J.E. French. 1996. Evaluation of transgenic mouse bioassays for identifying carcinogens and noncarcinogens. *Mutat.Res.* 365:119-127.

52. Tice, R.R., L.A. Nylander-French, and J.E. French. 1997. Absence of systemic in vivo genotoxicity after dermal exposure to ethyl acrylate and tripropylene glycol diacrylate in Tg.AC (v-Ha-ras) mice. *Environ.Mol.Mutagen.* 29:240-249.

53. Truett, T. 1998. Ethyl Acrylate. http://www.mc.vanderbilt.edu/vumcdept/derm/contact/ET007.html.

54. U.S.EPA (United States Environmental Protection Agency). 1998. TRIFacts Ethyl Acrylate. http://mail.odsnet.com/TRIFacts/108.html.

55. Udinsky, J. R., and C.B. Frederick. 1989. The enzymatic hydrolysis of ethyl acrylate by rat tissue homogenates. *The Toxicologist* 9:238.

56. USITC (United States International Trade Commission). 1990. Synthetic Organic Chemicals. *United States Production and Sales, 1989, Washington, DC*.

57. USITC (United States International Trade Commission). 1991. Synthetic Organic Chemicals. *United States Production and Sales, 1990, Washington, DC.*

58. USITC (United States International Trade Commission). 1992. Synthetic Organic Chemicals. *United States Production and Sales, 1991, Washington, DC*.

59. USITC (United States International Trade Commission). 1994. Synthetic Organic Chemicals. *United States Production and Sales, 1993, Washington, DC.*

60. Valencia, R., J.M. Mason, R.C. Woodruff, and S. Zimmering. 1985. Chemical mutagenesis testing in Drosophila. III. Results of 48 coded compounds tested for the National Toxicology Program. *Environ.Mutagen*. 7:325-348.

61. Verschueren, K. 1983. *Handbook of Chemical Data on Organic Chemicals*. New York: Van Nostrand Reinhold Company, Inc.

62. Waegemaekers, T.H., and M.P. Bensink. 1984. Non-mutagenicity of 27 aliphatic acrylate esters in the Salmonella-microsome test. *Mutat.Res*. 137:95-102.

63. Walker, A.M., A.J. Cohen, J.E. Loughlin, K.J. Rothman, and L.R. DeFonso. 1991. Mortality from cancer of the colon or rectum among workers exposed to ethyl acrylate and methyl methacrylate. *Scand.J.Work.Environ.Health* 17:7-19.

64. Weast, R. 1985. *CRC Handbook of Data on Organic Compounds.* Boca Raton: CRC Press, Inc.

65. Weast, R. 1986. *CRC Handbook of Chemistry and Physics*. Boca Raton: CRC Press, Inc.

66. Windholz, M. 1983. *The Merck Index*. Rahway: Merck & Company.

67. Zeiger, E., B. Anderson, S. Haworth, T. Lawlor, and K. Mortelmans. 1992. Salmonella mutagenicity tests: V. Results from the testing of 311 chemicals. *Environ.Mol.Mutagen.* 19 Suppl 21:2-141.

68. Zimmermann, F.K., and A. Mohr. 1992. Formaldehyde, glyoxal, urethane, methyl carbamate, 2,3-butanedione, 2,3-hexanedione, ethyl acrylate, dibromoacetonitrile and 2-hydroxypropionitrile induce chromosome loss in Saccharomyces cerevisiae. *Mutat.Res.* 270:151-166.

Appendix A - IARC Monographs. 1986. Vol 39, Sup 7: 81-98.

Some chemicals used in plastics and elastomers. IARC evalutation of the carinogenic risk of chemicals to humans.

ETHYL ACRYLATE

This substance was considered by a previous Working Group, in February 1978 (IARC, 1979). Since that time, new data have become available, and these have been incorporated into the monograph and taken into consideration in the present evaluation.

1. Chemical and Physical Data

1.1 Synonyms and trade names

Chem. Abstr. Services Reg. No.: 140-88-5

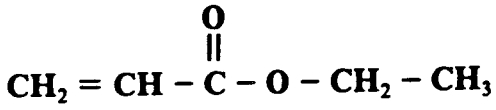
Chem. Abstr. Name: 2-Propenoic acid, ethyl ester

IUPAC Systematic Name: Ethyl acrylate

Synonyms: Acrylic acid, ethyl ester; European Council no. CE 245; ethoxycarbonylethylene; ethyl propenoate; ethyl 2-propenoate

Trade Names: Carboset 511; Latol 28-tall oil fatty acid

1.2 Structural and molecular formulae and molecular weight



$C_5H_8O_2$ Mol. wt: 100.13

1.3 Chemical and physical properties of the pure substance

(*a*) *Description*: Colourless liquid with an acrid penetrating odour (Hawley, 1981; Windholz, 1983; National Fire Protection Association, 1984; Sax, 1984) and reported odour thresholds of 1 ppb (4 $\mu g/m^3$) (Badische Corp. *et al.*, 1984) or 0.07 ppm (0.3 mg/m^3) (Stahl, 1973)

(*b*) *Boiling-point*: 99.8°C (Weast, 1984)

(*c*) *Melting-point*: -71.2°C (Weast, 1984)

(*d*) *Density*: d_4^{20} 0.9234 (Weast, 1984)

(*e*) *Spectroscopy data*: Ultraviolet (Grasselli & Ritchey, 1975), infrared (Sadtler Research Laboratories, 1980; prism [1310[a]], grating [29702]), nuclear magnetic resonance (Sadtler Research Laboratories, 1980; proton [7950, 7951], C-13 [2822]) and mass spectral data (NIH/EPA Chemical Information System, 1983) have been reported.

(*f*) *Solubility*: Slightly soluble in water (2 g/100 ml at 20°C); soluble in chloroform; miscible in ethanol and diethyl ether (Grasselli & Ritchey, 1975; Hawley, 1981; Windholz, 1983)

(*g*) *Volatility*: Vapour pressure, 29 mm Hg at 20°C; relative vapour density (air = 1), 3.5; saturation concentration, 158 g/m^3 at 20°C (Verschueren, 1983)

(*h*) *Stability*: Flash-point, 15.6°C (open-cup) (Windholz, 1983; National Fire Protection Association, 1984); polymerizes easily on standing, accelerated by heat, light and peroxides; vapour forms explosive mixtures in air (Hawley, 1981; Windholz, 1983; National Fire Protection Association, 1984); can react vigorously with oxidizing materials (Sax, 1984)

(*i*) *Conversion factor:* mg/m^3 = 4.10 × ppm[b]

1.4 Technical products and impurities

Commercial ethyl acrylate available in the USA has the following specifications: ethyl acrylate, 99.5 wt % min; water, 0.10 wt % max; acrylic acid, 0.009 wt % max; hydroquinone monomethyl ether (MEHQ), 15-20 mg/kg (also available with 50 or 200 mg/kg MEHQ or 1000 mg/kg hydroquinone (HQ)) and substantially free of suspended matter (Celanese Chemical Co., 1984). It is also available with the following specifications: ethyl acrylate, 99.5 wt % min; water, 0.05 wt %; acidity as acrylic acid, 0.005 wt %; HQ, 10-20, 90-120, 190-220, 470-530 or 900-1100 mg/kg; MEHQ, 10-20, 20-35, 40-60, 90-120, 190-220 or 470-530 mg/kg; HQ in MEHQ-inhibited product, 1.5 mg/kg max (Union Carbide Corp., 1982).

---

[a]Spectrum number in Sadtler compilation

[b]Calculated from: mg/m^3 = (molecular weight/24.45) × ppm, assuming standard temperature (25°C) and pressure (760 mm Hg)

Ethyl acrylate can undergo spontaneous polymerization. To prevent premature polymerization, inhibitors, such as HQ (see IARC, 1977) and MEHQ, are added and kept active under atmospheres containing 5-20% oxygen concentration in the vapour space. Polymerization is also inhibited by the exclusion of water and by keeping temperature below 25°C. When these precautions are taken, ethyl acrylate can be stored in tanks made of stainless-steel, aluminium or glass for up to six months. HQ and MEHQ can be removed from the ethyl acrylate prior to use in polymerization or neutralized by the addition of polymerization catalyst (Badische Corp. *et al.*, 1984).

2. Production, Use, Occurrence and Analysis

2.1 Production and use

(a) Production

Ethyl acrylate was first prepared by Redtenbacher in 1843 by oxidizing acrolein with silver oxide, then treating the silver salt with ethyl iodide. It has been produced commercially since the early 1930s (Luskin, 1970). In the USA, a propylene oxidation process is used almost exclusively for the production of acrylic compounds. This technique, developed commercially in 1970, involves the oxidation of propylene to acrolein and the subsequent oxidation of acrolein to acrylic acid. The reactions occur in the vapour phase in shell-and-tube exchangers at near atmospheric pressure. Bismuth/cobalt oxides on silica or alumina carrier are used as catalysts for the first oxidation reaction, and a molybdenum/vanadium system for the second. The acrylic acid leaving the second reactor is absorbed with water, extracted with an organic solvent and purified by vacuum distillation (Mannsville Chemical Products Corp., 1984). The ethyl ester is formed by reacting acrylic acid with ethanol.

A technique used in the past is the modified Reppe process, in which ethyl acrylate is produced by the reaction of acetylene with nickel carbonyl (see IARC, 1976) and ethanol in the presence of an acid. In a variation of this process, a company in the Federal Republic of Germany combines acetylene, carbon monoxide and water in the presence of a nickel halide to form acrylic acid. Ethanol is used to produce the ethyl ester.

Two techniques have been developed recently for the production of acrylate esters. One involves use of organic carbonates as esterifying agents, and the other yields acrylate esters from 2-halo-1-alkenes isolated from hydrocarbon feedstocks (Haggin, 1985).

There were four major producers of ethyl acrylate in the USA in 1984. The US International Trade Commission (1984) reported production of 131 million kg in 1983.

One company in France produced 60 million kg in 1984. This company and two companies in the Federal Republic of Germany have been identified as the primary producers of ethyl acrylate in western Europe.

In Japan, about 15 million kg ethyl acrylate were used in 1982 (Anon., 1983). There are currently four major producers of ethyl acrylate in Japan.

(*b*) *Use*

Acrylic esters undergo polymerization with water to form emulsion polymers, and these are the primary form in which acrylic monomers are used. When the emulsion, or substance containing an emulsion polymer, such as paint or adhesives, is applied to a surface, the water evaporates, leaving a tough film. Acrylic emulsion polymers are used in coatings, textiles, paper, adhesives, leather, polishes and sealants (Mannsville Chemical Products Corp., 1984).

Coatings

Acrylic polymers in latex paint form a coating that is resistant to water, sunlight and weather but remains flexible at low temperatures (Union Carbide Corp., 1982). Acrylic emulsion polymers are also used as industrial finishes and in can and coil coatings.

Textiles

Acrylic resin emulsion polymers are used in textile finishing to impart texture to fabric. They can be used to improve the abrasion and dirt resistance of fabric as well as for bonding, laminating and back coating. They have been used as binders in pigments and nonwoven fabric.

Paper

Paper coated with a suspension of acrylic emulsion polymers and finely ground solids is receptive to ink and water resistant (Mannsville Chemical Products Corp., 1984). Such coatings are used most often for book and magazine stock, but also for business machine paper, folding boxboard and frozen-food packaging. These emulsions can be added to paper pulp to impart resistance to grease and oil.

Adhesives

Acrylic emulsions are used as resins in adhesives on envelopes, labels and decals (Mannsville Chemical Products Corp., 1984). Emulsion-based sealants are also used for bathtub caulk, baseboard seams and glazing; sealants with acrylic solvents are found in skylight joints, concrete roofing and exterior panel joints.

Leather

Emulsion polymers bind topcoatings to leather and prevent their migration; they are used in automotive upholstery, furniture, clothing and shoes.

Foods and cosmetics

Ethyl acrylate has been used as a fragrance additive in some soaps, detergents, creams, lotions (at levels of 0.001-0.01%) and perfumes (at levels of 0.04-0.4%) and as a synthetic fruit essence (Opdyke, 1975).

(*c*) *Regulatory status and guidelines*

Occupational exposure limits for ethyl acrylate have been set by 13 countries by regulation or recommended guideline (Table 1).

Table 1. National occupational exposure limits for ethyl acrylate[a]

Country	Year	Concentration (mg/m³)	Interpretation[b]
Australia	1978	100	TWA
Belgium	1978	100[c]	TWA
Finland	1981	20[c]	TWA
Germany, Federal Republic of	1984	100[c]	TWA
Italy	1978	40[c]	TWA
The Netherlands	1978	100[c]	TWA
Romania	1975	50	TWA
		80	Ceiling
Sweden	1984	40[c]	TWA
Switzerland	1978	100[c]	TWA
UK	1985	100[c]	TWA
USA			
ACGIH	1984	20[c]	TWA
		100[c]	STEL
OSHA	1983	100[c]	TWA
Yugoslavia	1971	100	Ceiling

[a]From International Labour Office (1980); Työsuojeluhallitus (1981); US Occupational Safety and Health Administration (OSHA) (1983); American Conference of Governmental Industrial Hygienists (ACGIH) (1984); Arbetarskyddsstyrelsens Författningssamling (1984); Deutsches Forschungsgemeinschaft (1984); Health and Safety Executive (1985)

[b]TWA, time-weighted average; STEL, short-term exposure limit

[c]Skin notation (absorption is possible)

The Council of Europe (Conseil de l'Europe, 1981) included ethyl acetate in a list of artificial flavouring substances that may be added to foodstuffs without hazard to public health at a level of 1 ppm (mg/kg) in food and 0.2 mg/l in beverages.

The US Food and Drug Administration (1984) considers ethyl acrylate to be a 'generally recognized as safe' (GRAS) synthetic flavouring substance or food adjuvant. Ethyl acrylate polymers or copolymers are permitted as components of adhesives, resinous and polymeric coatings, paper and paperboard in contact with dry, aqueous or fatty foods, and semirigid and rigid acrylic and modified acrylic plastics. Homopolymers and acrylic copolymers of ethyl acrylate may be used as modifiers in semirigid and rigid vinyl chloride plastics.

Ethyl acrylate is classified as a hazardous waste by the US Environmental Protection Agency (1984) under the Resource Conservation and Recovery Act of 1976.

2.2 Occurrence

(*a*) *Natural occurrence*

Ethyl acrylate has been identified at low levels (0.77 mg/kg) in the volatile components of fresh pineapple (Haagen-Smit *et al.*, 1945; Näf-Müller & Willhalm, 1971).

(*b*) *Occupational exposure*

Ethyl acrylate was detected in the air in a pilot production and processing plant at concentrations of 4-58 mg/m^3 (Kuzelová *et al.*, 1981) and in the air of the resin department of a paint manufacturing facility at concentrations of <1-24 mg/m^3 (Belanger & Coye, 1981).

Mean time-weighted average (TWA) concentrations of ethyl acrylate monomer in air collected in areas near chemical reactors in a polystyrene production plant were 0.06-0.2 mg/m^3 for personal breathing zone samples and 0.012-0.1 mg/m^3 for work area samples. At an outdoor unloading site for lorries and containers, the TWA concentration of ethyl acrylate was as high as 230 mg/m^3 (Samimi & Falbo, 1982). At a resin manufacturing plant, concentrations of 49-2750 mg/m^3 ethyl acrylate monomer were measured in air emitted from a scrubber stack designed to prevent the exit of concentrations in excess of 40 mg/m^3 (Jones *et al.*, 1981).

Ethyl acrylate has been detected as a residual monomer in polyethyl acrylate (Brunn *et al.*, 1975) and, at a concentration of 50 mg/kg, in aqueous polymer latexes used in the paper and textile industries (Bollini *et al.*, 1975).

2.3 Analysis

Ethyl acrylate has been determined in air after adsorption onto charcoal, desorption with a solvent (carbon disulphide) and analysis by gas chromatography with flame ionization detection. This method was validated by the National Institute for Occupational Safety and Health for a range of 50-210 mg/m^3 (Taylor, 1977). The same method is used to measure ethyl acrylate after personal sampling for workplace exposures using passive dosimeters (Samimi & Falbo, 1983).

Carbon dioxide laser absorption spectroscopy can be used to detect ethyl acrylate in humid air at levels down to approximately 0.08 mg/m^3 (Loper *et al.*, 1982).

3. Biological Data Relevant to the Evaluation of Carcinogenic Risk to Humans

3.1 Carcinogenicity studies in animals

(*a*) *Oral administration*

Mouse: Groups of 50 male and 50 female B6C3F$_1$ mice, seven weeks of age, received 100

or 200 mg/kg bw ethyl acrylate (purity, 99-99.5% stabilized with 15 mg/kg of the monomethyl ether of hydroquinone) in 10 ml/kg bw corn oil by gavage five times per week for 103 weeks. Similar groups of mice received corn oil only and served as vehicle controls. The experiment was terminated 104-106 weeks after the beginning of the treatment. Survival in the control, low-dose and high-dose groups was: males, 56%, 72% and 60%; females, 54%, 70% and 52%, respectively. The incidences of squamous-cell carcinomas of the forestomach in the control, low-dose and high-dose male mice were: 0/48, 2/47 and 5/50 ($p = 0.03$, Fisher exact test, high-dose *versus* control; $p = 0.019$, Cochran-Armitage test for trend). The combined incidences of squamous-cell papillomas and carcinomas of the forestomach in the control, low-dose and high-dose groups were: males, 0/48, 5/47 and 12/50 ($p < 0.001$, high-dose *versus* control, Fisher exact test and trend test); females, 1/50, 5/49 and 7/48 ($p = 0.026$, high-dose *versus* control, Fisher exact and 0.022, trend test). Dose-related increases were observed in the incidence of non-neoplastic lesions (hyperkeratosis, hyperlasia and inflammation) in the forestomach [see also section 3.2(*a*)] in animals of each sex (National Toxicology Program, 1983).

Rat: Groups of 50 male and 50 female Fischer 344/N rats, seven weeks of age, received 100 or 200 mg/kg bw ethyl acrylate (purity, 99-99.5%, stabilized with 15 mg/kg of the monomethyl ether of hydroquinone) in 5 ml/kg bw corn oil by gavage five times per week for 103 weeks. Similar groups of rats received corn oil only and served as vehicle controls. The experiment was terminated 104-105 weeks after the beginning of the treatment. Survival in the control, low-dose and high-dose groups was: males, 82%, 64% and 68%; females, 72%, 72% and 84%. The incidences of squamous-cell carcinomas of the forestomach in the control, low-dose and high-dose male rats were: 0/50, 5/50 and 12/50 ($p < 0.001$, Fisher exact test, high-dose *versus* control, and Cochran-Armitage test for trend). The combined incidences of squamous-cell papillomas and carcinomas of the forestomach in the control, low-dose and high-dose groups were: males, 1/50, 18/50 and 36/50 ($p < 0.001$, Fisher exact test, high-dose *versus* control, and Cochran Armitage test for trend); females, 1/50, 6/50 and 11/50 ($p = 0.002$, Fisher exact test, high-dose *versus* control, and Cochran-Armitage test for trend), respectively. Dose-related increases were observed in the incidence of non-neoplastic lesions (hyperkeratosis, hyperplasia and inflammation) in the forestomach [see also section 3.2(*a*)] in animals of each sex (National Toxicology Program, 1983).

Groups of 25 male and 25 female young Wistar rats received 0, 6-7, 60-70 or 2000 mg/l (ppm) ethyl acrylate [purity unspecified] in the drinking-water for two years. After two years of treatment, survival was: males, 52%, 48%, 60% and 72%; females, 64%, 72%, 36% and 60%, in the control, low-, mid- and high-dose groups, respectively. No treatment-related lesion was reported (Borzelleca *et al.*, 1964). [The Working Group noted the incomplete description of the findings in this study.]

(*b*) *Skin application*

Mouse: A group of 40 male C3H/HeJ mice, 74-79 days of age, received thrice-weekly skin applications of 25 µl undiluted ethyl acrylate (purity, >99%) on the back skin for life (approximately 23 mg per application; total dose, approximately 770 mg/kg bw). Control

groups were treated either with acetone or with 0.1% 3-methylcholanthrene in acetone. The mean survival time of animals in the ethyl acrylate-treated group (408 days) did not differ significantly from that in the acetone controls (484 days). Complete necropsies were performed, and dorsal skin from all animals as well as gross lesions were examined histologically. No treatment-related tumour was observed in either ethyl acrylate- or acetone-treated mice; skin tumours (mainly squamous-cell carcinomas) were observed in 39/40 mice treated with 3-methylcholanthrene (DePass *et al.*, 1984). [The Working Group noted that no mention was made of control for possible losses of the parent compound by volatilization or polymerization.]

(*c*) *Inhalation exposure*

Mouse: Groups of 105 female and 105 male B6C3F$_1$ mice, seven to nine weeks of age, were exposed to vapours of ethyl acrylate (purity, >99.5%) at concentrations of 100, 310 or 920 mg/m^3 [25, 75 or 225 ppm] for 6 h per day on five days per week. The treatment with the low and medium doses lasted 27 months, whereas high-dose treatment was discontinued after six months due to a significant decrease in body-weight gain. These animals were followed without further treatment for up to 27 months. Two concurrent control groups, each of 84 female and 84 male untreated mice, were used. Interim sacrifices of small groups of exposed and control animals were made at six, 12 and 18 months, such that groups of approximately 75 animals per sex in the exposed group and 60 animals per sex in the control groups were available for the full study. The mean body-weight gains of both male and female mice in the mid- and high-dose groups were significantly lower than for the control groups throughout the study. Survival in all groups was adequate for evaluation of late-appearing tumours. No treatment-related increase in the incidence of tumours was observed, with the exception of thyroid follicular adenomas, which were increased in high-dose male mice when compared to concurrent but not historical controls (2/121 in concurrent controls; 16% in historical controls; and 7/69 in high-dose males). Dose-related increases were observed in the incidence of non-neoplastic lesions of the olfactory mucosa (glandular hyperplasia and metaplasia) in animals of each sex [see also section 3.2(*a*)] (Miller *et al.*, 1985).

Rat: Groups of 115 female and 115 male Fischer 344 rats, seven to nine weeks of age, were exposed to vapours of ethyl acrylate (purity, >99.5%) at concentrations of 100, 310 or 920 mg/m^3 [25, 75 or 225 ppm] for 6 h per day on five days per week. The treatment with the low- and mid-doses lasted 27 months, whereas the high-dose treatment was discontinued after six months due to a significant decrease in body-weight gain. These animals were followed without further treatment for up to 27 months. Two concurrent control groups, each of 92 female and 92 male untreated rats, were used. Interim sacrifices of small groups of exposed and control rats were made after three, six, 12 and 18 months of exposure, such that 75 animals per sex in the exposed groups and 60 animals per sex in the control groups were available for the full study. The mean body-weight gains of both male and female rats in the mid- and high-dose groups were significantly lower than for the control groups throughout the study. Survival in all exposed groups was adequate for the evaluation of late-appearing tumours. No treatment-related neoplastic lesion was observed at any dose level. Dose-related increases were observed in the incidence of non-neoplastic lesions of the olfactory

mucosa (glandular and basal-cell hyperplasia and metaplasia) in animals of each sex [see also section 3.2(*a*)] (Miller *et al.*, 1985).

3.2 Other relevant biological data

The toxic effects of acrylic monomers, including ethyl acrylate, have been reviewed (Autian, 1975)

(*a*) *Experimental systems*

Toxic effects

The oral LD_{50} for ethyl acrylate (in various solvents, sometimes unspecified) in rats has been reported to range from 1 g/kg bw (Pozzani *et al.*, 1949; Paulet & Vidal, 1975; Sandmeyer & Kirwin, 1981) to 2 g/kg bw (Union Carbide Corp., 1971). The oral LD_{50} is 1.8 g/kg bw in male ddY mice (Tanii & Hashimoto, 1982) and 400 mg/kg bw in rabbits (Fassett, 1963). Intraperitoneal LD_{50}s are 450 mg/kg bw in Wistar rats (Paulet & Vidal, 1975) and 600 mg/kg bw in male ICR mice (Lawrence *et al.*, 1972). The dermal LD_{50} in rabbits has been reported to be 1.8-2 g/kg bw (undiluted) (Pozzani *et al.*, 1949; Union Carbide Corp., 1971).

LC_{50} values for 4-h exposure have been reported to range from <4100-8200 mg/m^3 (<1000-2000 ppm) in rats (Pozzani *et al.*, 1949; Fassett, 1963), from <4100-16 400 mg/m^3 (<1000-4000 ppm) in rabbits (Sandmeyer & Kirwin, 1981) and to be 3950 ppm (16 200 mg/m^3) in mice (Lomonova & Klimova, 1979).

Early studies of the inhalation toxicity of ethyl acrylate vapours in small numbers of rats, rabbits, guinea-pigs and monkeys reported signs of acute irritation in the lung and upper respiratory tract at concentrations of 1230 and 2200 mg/m^3 (300 and 540 ppm) (Pozzani *et al.*, 1949) or 4940 mg/m^3 (1204 ppm) (Treon *et al.*, 1949).

Male and female Fischer 344 rats and B6C3F1 mice exposed to 100-920 mg/m^3 (25-225 ppm) ethyl acrylate vapours for 6 h per day on five days per week for up to 27 months developed selective histopathological changes of the nasal mucosa (hyperplasia of submucosal glands and respiratory metaplasia of the olfactory epithelium) (Miller *et al.*, 1985).

Male and female Fischer 344 rats and B6C3F$_1$ mice were given 100, 200, 400, 600 or 800 mg/kg bw ethyl acrylate in corn oil by gavage. After 14 days, rats developed abdominal adhesions (at 600 and 800 mg/kg) and tissue lesions of the forestomach (at 400 mg/kg), characterized histologically as hyperkeratosis, hyperplasia and inflammation. Inflammation of the forestomach was seen in mice (at 400 and 600 mg/kg). Such lesions were not found at doses of 100 and 200 mg/kg (National Toxicology Program, 1983; Ghanayem *et al.*, 1985a,b).

Fischer 344 rats and B6C3F$_1$ mice of each sex that received 100 or 200 mg/kg bw ethyl acrylate by gavage five times per week for 103 weeks showed epithelial hyperplasia of the forestomach, usually associated with variable degrees of hyperkeratosis (see also section 3.1) (National Toxicology Program, 1983).

When applied to the skin of rabbits, ethyl acrylate caused marked local irritation, erythema, oedema and vascular damage (Treon *et al.*, 1949).

With the guinea-pig 'maximization test' (intradermal injections of acrylate in peanut oil, acrylate in Freund's complete adjuvant (FCA) and FCA alone) and the FCA test (see Klecak *et al.*, 1977), ethyl acrylate was shown to be a sensitizing agent (van der Walle *et al.*, 1982). Guinea-pigs sensitized to ethyl acrylate showed cross reactions to other monoacrylates (van der Walle & Bensink, 1982).

When undiluted ethyl acrylate was applied to the skin of 40 male C3H/HeJ mice at a dose of 25 μl (23 mg/mouse per application) three times weekly for life, histological skin changes were observed, including epidermal necrosis (four animals), keratin necrosis (six animals), dermal fibrosis (six animals), hyperkeratosis (12 animals) and dermatitis (five animals) (DePass *et al.*, 1984).

Effects on reproduction and prenatal toxicity

Groups of 10-23 pregnant Wistar rats received oral doses of 0, 25, 50, 100, 200 or 400 mg/kg bw per day ethyl acrylate [solvent unspecified] on gestation days 7-16. Maternal body weights were reduced (but not in a dose-related manner) in treated groups. The total number of resorptions was significantly increased with the three highest doses, but the number of live foetuses per litter was not significantly affected. When 50% of foetuses were examined for skeletal defects, the overall incidence of delayed ossification was found to be increased in all treated groups (Pietrowicz *et al.*, 1980).

In an inhalation study, Murray *et al.* (1981) exposed pregnant Sprague-Dawley rats to 0, 205 or 615 mg/m^3 (0, 50 or 150 ppm) ethyl acrylate vapour for 6 h per day on gestation days 6-15. Maternal toxicity at 615 mg/m^3 (150 ppm) was reflected in reduced food consumption and body-weight gain. In the foetuses, no significant increase was seen in gross, visceral or skeletal malformations at either exposure level, although three foetuses in three litters (10% of litters) in the 615-mg/m^3 (150-ppm) group had hypoplastic tail and associated skeletal defects. Historically, this defect had been noted in 1% of over 800 control litters, and the highest incidence in one control group was 7% of litters.

Absorption, distribution, excretion and metabolism

After administration of 200 mg/kg bw ethyl acrylate in corn oil by gavage to Fischer 344 rats, no trace of the compound was found in blood samples from the retro-orbital venous plexus after 15, 30 or 60 min (detection limit, 1 μg/ml); however, detectable amounts were present in the portal venous blood after 15 or 30 min (up to 27 μg/ml). This may indicate that, after absorption, ethyl acrylate is hydrolysed rapidly in the blood and/or liver and does not circulate through the body (National Toxicology Program, 1983). In-vitro experiments also indicate that ethyl acrylate binds to nonprotein sulfhydryls in erythrocytes (Miller *et al.*, 1981).

After administration to Fischer 344 rats of 100 mg/kg bw ethyl acrylate as a 2% solution in corn oil by gavage, 30-32% of the dose remained in the stomach after 30 min and 21-27% after 2 h (National Toxicology Program, 1983). The in-vivo concentration of nonprotein sulfhydryls in the forestomach (National Toxicology Program, 1983), lungs, blood and liver (Silver & Murphy, 1978) was reduced.

Intraperitoneal injection to Wistar rats of 70 mg/kg bw ethyl acrylate (in peanut oil) resulted in the excretion of thioethers in the urine, probably as mercapturic acids or related conjugates [not identified]. Inhibition of esterases by pretreatment with tri-*ortho*-tolyl phosphate (TOTP) resulted in an approximately six-fold increase in thioether excretion after the same dose of ethyl acrylate (Delbressine, 1981). Ethyl acrylate-induced depletion of nonprotein sulfhydryls *in vivo* in rats appeared to be more pronounced after TOTP treatment (Silver & Murphy, 1978).

Nonenzymatic and enzymatic hydrolysis of ethyl acrylate to acrylic acid was demonstrated to occur *in vitro* in plasma and homogenates of rat forestomach, glandular stomach, stomach contents, liver, lung and kidney (Silver & Murphy, 1978; Miller *et al.*, 1981; National Toxicology Program, 1983).

Ethyl acrylate binds to glutathione *in vitro* both spontaneously and after catalysis by liver glutathione-*S*-transferase (Miller *et al.*, 1981).

Mutagenicity and other short-term tests

Ethyl acrylate (tested at up to 10 000 μg/plate) was not mutagenic to *Salmonella typhimurium* TA1535, TA1537, TA1538, TA98 or TA100 in the presence or absence of a metabolic system (S9) from the liver of polychlorinated biphenyl-induced rats and hamsters or phenobarbital-induced rats, when tested in liquid incubation and plate incorporation assays (Ishidate *et al.*, 1981 [details not given]; Haworth *et al.*, 1983; National Toxicology Program, 1983; Waegemaekers & Bensink, 1984). [The Working Group noted that only in the study by Waegemaekers & Bensink were the conditions used appropriate to the testing of a volatile compound.]

Ethyl acrylate did not induce sex-linked recessive lethal mutations in *Drosophila melanogaster* when injected (20 mg/ml) or administered in feed (40 000 ppm [mg/kg]) (Valencia *et al.*, 1985).

Ethyl acrylate (7.5-15 μg/ml) induced a dose-related increase in the incidence of chromosomal aberrations in cultured Chinese hamster lung cells in the absence of a metabolic system (Ishidate, 1983).

Groups of four male Balb/c mice were given two intraperitoneal injections (24 h apart) of ethyl acrylate (total dose, 225-1800 mg/kg bw), and the bone marrow was harvested 6 h after the second injection; a dose-related increase in the number of micronucleated polychromatic erythrocytes was observed (Przybojewska *et al.*, 1984).

(*b*) *Humans*

Toxic effects

Ethyl acrylate is irritating to the skin, eyes and mucous membranes of the gastrointestinal tract and respiratory system (Nemec & Bauer, 1978). A dose of 4% in petrolatum produced sensitization reactions in 10/24 volunteers; no irritation was observed in 48-h closed patch tests (Opdyke, 1975).

Prolonged exposure to 205-308 mg/m^3 (50-75 ppm) ethyl acrylate produced drowsiness, headache and nausea (Nemec & Bauer, 1978). Fourteen of 33 workers exposed over an

average period of five years to 4-58 mg/m³ ethyl acrylate (and 50 mg/m³ butyl acrylate) complained of autonomic and neurotic symptoms, but electroencephalographic examination showed no organic dysfunction (Kuželová *et al.*, 1981).

Effects on reproduction and prenatal toxicity

No data were available to the Working Group.

Absorption, distribution, excretion and metabolism

No data were available to the Working Group.

Mutagenicity and chromosomal effects

No data were available to the Working Group.

3.3 Case reports and epidemiological studies of carcinogenicity to humans

No data were available to the Working Group.

4. Summary of Data Reported and Evaluation

4.1 Exposure data

Ethyl acrylate has been produced commercially since the early 1930s. Occupational exposure occurs in the manufacture of ethyl acrylate and in the manufacture and use of its emulsion polymers. It is also used as a synthetic flavouring substance and fragrance adjuvant in consumer products.

4.2 Experimental data

Ethyl acrylate was tested for carcinogenicity by gavage in mice and rats. Dose-related increases in the incidence of squamous-cell papillomas and carcinomas of the forestomach were observed in both species. Ethyl acrylate was tested by inhalation in the same strains of mice and rats; no treatment-related neoplastic lesion was observed. No treatment-related tumour was observed following skin application of ethyl acrylate for lifespan to male mice.

In one experiment in rats, oral administration of ethyl acrylate produced signs of embryotoxicity and foetotoxicity at mildly maternally toxic doses but did not increase foetal malformation. It was not embryotoxic, foetotoxic or teratogenic to rats at an airborne concentration that produced slight maternal toxicity.

Ethyl acrylate was not mutagenic to *Salmonella typhimurium* in the presence or absence of an exogenous metabolic system, nor was it mutagenic to *Drosophila melanogaster*. It induced chromosomal aberrations in Chinese hamster lung cells *in vitro* and micronuclei in the bone marrow of mice treated *in vivo*.

Overall assessment of data from short-term tests: Ethyl acrylate[a]

	Genetic activity			Cell transformation
	DNA damage	Mutation	Chromosomal effects	
Prokaryotes		–		
Fungi/ Green plants				
Insects		–		
Mammalian cells (*in vitro*)			+	
Mammals (*in vivo*)			+	
Humans (*in vivo*)				
Degree of evidence in short-term tests for genetic activity: **Limited**				Cell transformation: No data

[a]The groups into which the table is divided and the symbols '+', '–' and '?' are defined on pp. 19-20 of the Preamble; the degrees of evidence are defined on pp. 20-21.

4.3 Human data

No data were available to evaluate the reproductive effects or prenatal toxicity of ethyl acrylate to humans.

No case report or epidemiological study was available to evaluate the carcinogenicity of ethyl acrylate to humans.

4.4 Evaluation[1]

There is *sufficient evidence*[2] for the carcinogenicity of ethyl acrylate in experimental animals.

No data on humans were available.

---

[1]For definition of the italicized term, see Preamble, p. 18.

[2]In the absence of data on humans, it is reasonable, for practical purposes, to regard chemicals for which there is sufficient evidence of carcinogenicity in animals as if they presented a carcinogenic risk to humans.

5. References

American Conference of Governmental Industrial Hygienists (1984) *Threshold Limit Values for Chemical Substances and Physical Agents in the Work Environment and Biological Exposure Indices with Intended Changes for 1984-85*, Cincinnati, OH, p. 18

Anon. (1983) Acrylate ester promising. *Plast. Ind. News, 29*, 97-98

Arbetarskyddsstyrelsens Författningssamling (National Swedish Board of Occupational Safety and Health) (1984) *Hygienic Limit Values (AFS 1984:5)* (Swed.), Stockholm, p. 16

Autian, J. (1975) Structure-toxicity relationships of acrylic monomers. *Environ. Health Perspect., 11*, 141-152

Badische Corp., Celanese Chemical Co., Inc., Rohm & Haas Co. & Union Carbide Corp. (1984) *Acrylate Esters, A Guide to Safety and Handling*, Williamsburg, VA, Dallas, TX, Philadelphia, PA, Danbury, CT

Belanger, P.L. & Coye, M.J. (1981) *Health Hazard Evaluation Report No. HHE-80-68-871 Sinclair Paint Company, Los Angeles, CA (US NTIS PB82-214396)*, Washington DC, US Department of Health and Human Services, Public Health Service, Centers for Disease Control, National Institute for Occupational Safety and Health

Bollini, M., Seves, A. & Focher, B. (1975) Determination of free monomers in aqueous emulsions of synthetic polymers and copolymers (Ital.). *Textilia, 51*, 25-28

Borzelleca, J.F., Larson, P.S., Hennigar, G.R., Jr, Huf, E.G., Crawford, E.M. & Blackwell Smith, R., Jr (1964) Studies on the chronic oral toxicity of monomeric ethyl acrylate and methyl methacrylate. *Toxicol. appl. Pharmacol., 6*, 29-36

Brunn, J., Doerffel, K., Much, H. & Zimmermann, G. (1975) Ultraviolet photometric determination of residual monomer content in technical polymers of acrylic acids and acrylic acid ethyl esters (Ger.). *Plaste Kautsch., 22*, 485-486 [*Chem. Abstr., 83*, 115163m]

Celanese Chemical Co. (1984) *Ethyl Acrylate Sales Specifications (Technical Bulletin No. CCC-92)*, Dallas, TX

Conseil de l'Europe (1981) *Substances Aromatisantes et Sources Naturelles de Matières Aromatisantes* (Flavouring substances and natural occurrence of flavouring materials), Moulin-les-Metz, Maisonneuve

Delbressine, L.P.C. (1981) *Metabolic Detoxification of Olefinic Compounds*, PhD Thesis, Nijmegen, University of Nijmegen, The Netherlands, p. 99

DePass, L.R., Fowler, E.H., Meckley, D.R. & Weil, C.S. (1984) Dermal oncogenicity bioassays of acrylic acid, ethyl acrylate, and butyl acrylate. *J. Toxicol. environ. Health, 14*, 115-120

Deutsche Forschungsgemeinschaft (1984) *Maximal Concentrations in the Workplace and Biological Occupational Limit Value* (Ger.), Part XX, Weinheim, Verlag Chemie GmbH, p. 34

Fassett, D.W. (1963) *Esters.* In: Patty, F.A., ed., *Industrial Hygiene and Toxicology*, 2nd rev. ed., Vol. 2, New York, Interscience, pp. 1877-1880

Ghanayem, B.I., Maronpot, R.R. & Matthews, H.B. (1985a) Ethyl acrylate-induced gastric toxicity. I. Effect of single and repetitive dosing. *Toxicol. appl. Pharmacol., 80*, 323-335

Ghanayem, B.I., Maronpot, R.R. & Matthews, H.B. (1985b) Ethyl acrylate-induced gastric toxicity. II. Structure-toxicity relationships and mechanisms. *Toxicol. appl. Pharmacol., 80*, 336-344

Grasselli, J.G. & Ritchey, W.M., eds (1975) *CRC Atlas of Spectral Data and Physical Constants for Organic Compounds*, Vol. 4, Cleveland, OH, CRC Press, p. 314

Haagen-Smit, A.J., Kirchner, J.G., Prater, A.N. & Deasy, C.L. (1945) Chemical studies of pineapple (*Ananas sativas* Lindl). I. The volatile flavor and odor constituents of pineapple. *J. Am. chem. Soc., 67*, 1646-1650

Haggin, J. (1985) New Dow acrylate ester processes derive from C_1 efforts. *Chem. Eng. News, 63*, 25-26

Hawley, G.G., ed. (1981) *The Condensed Chemical Dictionary*, 10th ed., New York, Van Nostrand Reinhold Co., pp. 422-423

Haworth, S., Lawlor, T., Mortelmans, K., Speck, W. & Zeiger, E. (1983) *Salmonella* mutagenicity test results for 250 chemicals. *Environ. Mutagenesis, Suppl. 1*, 3-142

Health and Safety Executive (1985) *Occupational Exposure Limits 1985* (*Guidance Note EH 40/85*), London, Her Majesty's Stationery Office, p. 13

IARC (1976) *IARC Monographs on the Evaluation of Carcinogenic Risk of Chemicals to Man*, Vol. 11, *Cadmium, Nickel, Some Epoxides, Miscellaneous Industrial Chemicals and General Considerations on Volatile Anaesthetics*, Lyon, pp. 75-112

IARC (1977) *IARC Monographs on the Evaluation of the Carcinogenic Risk of Chemicals to Man*, Vol. 15, *Some Fumigants, the Herbicides 2,4-D and 2,4,5-T, Chlorinated Dibenzodioxins and Miscellaneous Industrial Chemicals*, Lyon, pp. 155-175

IARC (1979) *IARC Monographs on the Evaluation of the Carcinogenic Risk of Chemicals to Humans*, Vol. 19, *Some Monomers, Plastics and Synthetic Elastomers, and Acrolein*, Lyon, pp. 57-71

International Labour Office (1980) *Occupational Exposure Limits for Airborne Toxic Substances, A Tabular Compilation of Values from Selected Countries*, 2nd (rev.) ed. (*Occupational Safety and Health Series No. 37*), Geneva, pp. 110-111

Ishidate, M., Jr and staff, eds (1983) *The Data Book of Chromosomal Aberration Tests* In Vitro *on 587 Chemical Substances Using a Chinese Hamster Fibroblast Cell Line (CHL Cells)*, Tokyo, The Realize Inc., p. 197

Ishidate, M., Jr, Sofuni, T. & Yoshikawa, K. (1981) Chromosomal aberration tests *in vitro* as a primary screening tool for environmental mutagens and/or carcinogens. *Gann Monogr. Cancer Res., 27*, 95-108

Jones, M.T., Pilgrim, R.C. & Murrow, P.J. (1981) *Control of acrylic monomer emissions from a process situated in a sensitive area.* In: Webb, K.A. & Smith, A.J., eds, *Proceedings of the Seventh International Clean Air Conference, Adelaide, Australia*, Ann Arbor, MI, Ann Arbor Science, pp. 809-827

Klecak, G., Geleick, H. & Frey, J.R. (1977) Screening of fragrance materials for allergenicity in the guinea pig. I. Comparison of four testing methods. *J. Soc. cosmet. Chem., 28*, 53-64

Kuželová, M., Kovařík, J., Fiedlerová, D. & Popler, A. (1981) Acrylic compounds and general health of the exposed persons (Czech.). *Pracov. Lék., 33*, 95-99

Lawrence, W.H., Bass, G.E., Purcell, W.P. & Autian, J. (1972) Use of mathematical models in the study of structure-toxicity relationships of dental compounds: I. Esters of acrylic and methacrylic acids. *J. dent. Res., 51*, 526-535

Lomonova, G.V. & Klimova, E.I. (1979) Toxicity of methyl and ethyl acrylates (Russ.). *Gig. Tr. prof. Zabol., 9*, 55-56

Loper, G.L., Sasaki, G.R. & Stamps, M.A. (1982) Carbon dioxide laser absorption spectra of toxic industrial compounds. *Appl. Optics, 21*, 1648-1653

Luskin, L.S. (1970) *Acrylic acid, methacrylic acid, and the related esters.* In: Leonard, E.C., ed., *Vinyl and Diene Monomers*, Part 1, New York, Wiley Interscience, pp. 105-203

Mannsville Chemical Products Corp. (1984) *Acrylates and Acrylic Acid (Chemical Products Synopsis)*, Cortland, NY

Miller, R.R., Ayres, J.A., Rampy, L.W. & McKenna, M.J. (1981) Metabolism of acrylate esters in rat tissue homogenates. *Fundam. appl. Toxicol., 1*, 410-414

Miller, R.R., Young, J.T., Kociba, R.J., Keyes, D.G., Bodner, K.M., Calhoun, L.L. & Ayres, J.A. (1985) Chronic toxicity and oncogenicity bioassay of inhaled ethyl acrylate in Fischer 344 rats and B6C3F1 mice. *Drug chem. Toxicol., 8*, 1-42

Murray, J.S., Miller, R.R., Deacon, M.M., Hanley, T.R., Jr, Hayes, W.C., Rao, K.S. & John, J.A. (1981) Teratological evaluation of inhaled ethyl acrylate in rats. *Toxicol. appl. Pharmacol., 60*, 106-111

Näf-Müller, R. & Willhalm, B. (1971) On volatile constituents of pineapple (Ger.). *Helv. chim. Acta, 54*, 1880-1890

National Fire Protection Association (1984) *Fire Protection Guide on Hazardous Materials*, 8th ed., Quincy, MA, pp. 325M-47, 49-46 - 49-47

National Toxicology Program (1983) *NTP Technical Report on the Carcinogenesis Studies of Ethyl Acrylate (CAS No. 140-88-5) in F344/N Rats and B6C3F$_1$ Mice (Gavage Studies) (Technical Report Series No. 259)*, Research Triangle Park, NC

Nemec, J. & Bauer, W., Jr (1978) *Acrylic acid and derivates.* In: Mark, H.F., Othmer, D.F., Overberger, C.G. & Seaborg, G.T., eds, *Kirk-Othmer Encyclopedia of Chemical Technology*, 3rd ed., Vol. 1, New York, John Wiley & Sons, pp. 330-354

NIH/EPA Chemical Information System (1983) *Carbon-13 NMR Spectral Search System, Mass Spectral Search System,* and *Infrared Spectral Search System*, Arlington, VA, Information Consultants

Opdyke, D.L.J. (1975) Monographs on fragrance raw materials, ethyl acrylate. *Food Cosmet. Toxicol., 13* (Suppl.), 801-802

Paulet, G. & Vidal (1975) On the toxicity of some esters acrylic and methacrylic esters of acrylamide and polyacrylamides (Fr.). *Arch. Mal. prof., 36*, 58-60

Pietrowicz, D., Owecka, A. & Barański, B. (1980) Disturbances in rat's embryonal development due to ethyl acrylate. *Zwierzeta Lab., 17*, 67-72

Pozzani, U.C., Weil, C.S. & Carpenter, C.P. (1949) Subacute vapor toxicity and range-finding data for ethyl acrylate. *J. ind. Hyg. Toxicol., 31*, 311-316

Przybojewska, B., Dziubaltowska, E. & Kowalski, Z. (1984) Genotoxic effects of ethyl acrylate and methyl acrylate in the mouse evaluated by the micronucleus test. *Mutat. Res., 135*, 189-191

Sadtler Research Laboratories (1980) *The Sadtler Standard Spectra Collection, Cumulative Index*, Philadelphia, PA

Samimi, B. & Falbo, L. (1982) Monitoring of workers exposure to low levels of airborne monomers in a polystyrene production plant. *Am. ind. Hyg. Assoc. J., 43*, 858-862

Samimi, B. & Falbo, L. (1983) Validation of Abcor (NMS) organic vapor dosimeter under various concentrations and air velocity conditions. *Am. ind. Hyg. Assoc. J., 44*, 402-408

Sandmeyer, E.E. & Kirwin, C.J., Jr (1981) *Esters.* In: Clayton, G.D. & Clayton, F.E., eds, *Patty's Industrial Hygiene and Toxicology*, 3rd rev. ed., Vol. 2A, *Toxicology*, New York, John Wiley & Sons, p. 2294

Sax, N.I. (1984) *Dangerous Properties of Industrial Materials*, 6th ed., New York, Van Nostrand Reinhold, pp. 1315-1316

Silver, E.H. & Murphy, S.D. (1978) The effect of carboxylesterase inhibition on the toxicity of methyl acrylate, ethyl acrylate and acrylic acid (Abstract No. 216). *Toxicol. appl. Pharmacol., 45*, 312-313

Stahl, W.H., ed. (1973) *Compilation of Odor and Taste Threshold Values Data* (*ASTM Data Series DS 48*), Philadelphia, PA, American Society for Testing and Materials, p. 32

Tanii, H. & Hashimoto, K. (1982) Structure-toxicity relationship of acrylates and methacrylates. *Toxicol. Lett., 11*, 125-129

Taylor, D.G. (1977) *NIOSH Manual of Analytical Methods*, 2nd ed., Vol. 2 (*(NIOSH) DHEW Publ. No. 77-157-B*), Washington DC, US Government Printing Office, pp. S35-1 — S35-9

Treon, J.F., Sigmon, H., Wright, H. & Kitzmiller, K.V. (1949) The toxicity of methyl and ethyl acrylate. *J. ind. Hyg. Toxicol., 31*, 317-326

Työsuojeluhallitus (National Finnish Board of Occupational Safety and Health) (1981) *Airborne Contaminants in the Workplace* (*Safety Bull. 3*) (Finn.), Tampere, p. 13

Union Carbide Corp. (1971) *Toxicology Studies - Ethyl Acrylate*, New York, Industrial Medicine and Toxicology Department

Union Carbide Corp. (1982) *Product Information: Ethyl, Butyl and 2-Ethylhexyl Acrylates (Technical Bulletin No. F-40252C)*, Danbury, CT

US Environmental Protection Agency (1984) Protection of environment. *US Code Fed. Regul., Title 40*, Part 261.33, p. 364

US Food and Drug Administration (1984) Food and drugs. *US Code Fed. Regul., Title 21*, Parts 172.515, 175.105, 175.300, 176.170, 176.180, 177.1010, 178.3790, pp. 49, 133, 145, 188, 198

US International Trade Commission (1984) *Synthetic Organic Chemicals, US Production and Sales, 1983 (USITC Publication 1588)*, Washington DC, US Government Printing Office, p. 258

US Occupational Safety and Health Administration (1983) *General Industry. OSHA Safety and Health Standards (29 CFR 1910) (OSHA 2206)* (rev.), Washington DC, US Government Printing Office, p. 601

Valencia, R., Mason, J.M., Woodruff, R.C. & Zimmering, S. (1985) Chemical mutagenesis testing in *Drosophila*. III. Results of 48 coded compounds tested for the National Toxicology Program. *Environ. Mutagenesis, 7*, 325-348

Verschueren, K. (1983) *Handbook of Environmental Data on Organic Chemicals*, 2nd ed., New York, Van Nostrand Reinhold, pp. 625-626

Waegemaekers, T.H.J.M. & Bensink, M.P.M. (1984) Non-mutagenicity of 27 aliphatic acrylate esters in the *Salmonella*-microsome test. *Mutat. Res., 137*, 95-102

van der Walle, H.B. & Bensink, T. (1982) Cross reaction pattern of 26 acrylic monomers on guinea pig skin. *Contact Dermatol., 8*, 376-382

van der Walle, H.B., Klecak, G., Geleick, H. & Bensink, T. (1982) Sensitizing potential of 14 mono(meth)acrylates in the guinea pig. *Contact Dermatol., 8*, 223-235

Weast, R.C., ed. (1984) *CRC Handbook of Chemistry and Physics*, 65th ed., Boca Raton, FL, CRC Press, p. C-80

Windholz, M., ed. (1983) *The Merck Index*, 10th ed., Rahway, NJ, Merck & Co., p. 546